INDUSTRIALISATION
ITS CHALLENGE TO MEDICINE *

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INDUSTRIALISATION is by no means a synonym for civilisation. Many people today must have doubts about the benefits industrialisation bestows upon civilisation. Koreans, Laotians, and the Congolese, to mention a few, may be somewhat sceptical about the immediate advantages resulting from technological and political advancement. The jobless may find it difficult to equate an increase in gross national productivity with a commensurate increase in personal happiness. Though these examples may be somewhat extreme, they do illustrate the double-edged nature of industrialisation's impact on human society and its members.

Indices of Industrialisation

It is an easy matter to obtain data on a nation's industrial development. A seemingly inexhaustible supply of charts, graphs, and statistics will be supplied by a proud Government in response to the most tentative of inquiries. To obtain data on the effect industrialisation has on the people is a different matter. Such data can only be obtained from a variety of unrelated sources. The sources used, and the information obtained, frequently reflect the bias and prejudice of the investigator. It is quite understandable, under the circumstances, that an infinite number of judgmental pronouncements on psychosocial economic topics are made by innumerable self-appointed experts. These experts may be heads-of-States, sociologists, economists, playwrights, novelists, psychiatrists, columnists, and even ordinary physicians.

Psychosocial Pathology in Industrialised Societies

"Pathology" is the study of disease. "Psychopathology" is the study of emotional abnormalities. "Social pathology" is a term to describe behavioural abnormalities in human society. The early research into emotional disorders was patient-orientated. The knowledge obtained from these depth studies of the individual was gradually applied to the behaviour of human groups. The validity of such generalisations became apparent with the information gathered from workers in the fields of sociology and anthropology. This coming together of information from a variety of allied disciplines enabled a hitherto amorphous mass of fact, theory, and conjecture to be arranged in a meaningful concept—a concept that has enabled the physician to integrate the social, emotional, and environmental factors in his patient's illness under the term "psychosocial disease".[1] If there is disease there must also exist pathology—in this instance "psychosocial pathology".

Pathology of this type may be observed with infinite variety at all levels of human behaviour. In nations, communities, families, and individuals, the signs and symptoms of psychosocial pathology are in evidence.

Internationally the conflicting philosophies, ideologies, and political systems can be viewed as symptomatic of this pathological process. Our attempts to eradicate this pathology have met with little success. At present it seems to have the attributes of a cancerous growth and may prove lethal to its host—us! It is difficult to view with complacency our technological capacity to create a hell-fire on earth, far more horrific and spectacular than any envisaged by the prophets of old. Contemplation of such possibilities does not seem to ease international tensions, and it most certainly does not relieve individual fears.

Industrialisation with its ever-increasing efficiency is relegating to its human masters a role of ever-increasing insignificance. This becomes a matter of national concern. Work lay-offs reflecting the redundancy of man, and increasing automation reflecting the superiority of the machine, do not help to uphold "the dignity of man".[2] The nomads of the labour force seeking work compatible with their education and skills have become the concern of Governments, industry, and unions. The psychosocial-economic problems resulting from these technological developments and human displacements strain the resources of the nation's economy, its social and welfare organisations, and its professional health personnel.

Within the family unit evidence of the same pathology is apparent. In the face of international tension, and national uncertainty, the trend to early marriage, the rapid tempo of family formation, and the desire for the acquisition of the material comforts of life undoubtedly reflect a frantic wish to experience some of the benefits of modern living in an era when the future is by no means safe and assured.

To attain this ideal with the minimum of delay, it is essential to earn the maximum possible. No longer is the care of house, home, and family the sole responsibility of the wife and mother. The married woman with house and family is now an accepted member of the labour force. Her income is often an essential contribution to the family coffers. With shorter work weeks and an apparent inability or unwillingness to utilise leisure time in a conconstructive and satisfying manner, the leisure time is used up in moon-lighting or day-lighting. The effects, good or bad, on the family unit of all this activity are difficult to assess.

Indirect evidence of the deleterious effects of this desire to achieve "heaven on earth" as rapidly as possible can perhaps be detected in such indices of psychosocial pathology as juvenile-delinquency rates, marital break-ups, incidence of alcoholism, accidents, and the ebb-and-flow through our mental institutions.

Within the family unit still other changes reflect the impact of urbanisation and industrialisation on this basic human group. Today's family is neither matriarchal nor patriarchal. A companionship relationship exists between its members. This ill-defined relationship is not conducive to family cohesion. It is perhaps more anarchistic than

* Talk given to Canadian Mental Health Association, Calgary, March 27, 1961.

1. Halliday, J. L. Psycho-social Medicine. New York, 1948.

2. Report of Special Committee of the Senate of Canada on Manpower and Employment. Department of Labour, Ottawa, 1961.

democratic in attitudes and actions. Parental uncertainties are reflected in the loss of parental authority and respect by their offspring. The husband of today has, perhaps, become a father too early. The aggressive adventure-seeking male has been replaced by a security-seeking, home-based father-husband. The non-biological creative urges associated with the young male appear to have been expended in biological creativity.

The wife also exhibits symptoms from living in this era of rapid industrial change, uncertain future, and material plenty. She has been forced to assume some of the male stereotypes—physical strength, emotional resilience, and mental and economic self-sufficiency. Whether these added roles have been taken on gladly is debatable.[3] It may be assumed the female of the species still hankers after the traditional attributes of her sex—a wish to be loved, to be dependent on her mate, and to have a feeling of security in a home that has roots, not wheels.

Today's offspring reflect the doubts and uncertainties of their parents. The child and adolescent may react in several ways. They may remain docile and dependent. They may emulate the super-men of the mass media with pseudo self-reliance and overt hostility. Or they may, with or without parental encouragement, utilise the advantages of our industrialised society to advance themselves academically and vocationally. No matter how the offspring react, it would appear that the period of " emotional weaning " lengthens as industrialisation progresses, and preparation for entering an industrialised society becomes more complicated. This lengthening of the weaning process in conjunction with the shortening of the time for biological maturity adds further problems to an already complicated psychosocial situation.

General Remarks

The change to industrial living has not been accomplished without considerable turmoil in those exposed to the transition. With improved technology, not only has the rate of transition increased but the material advantages from technology are now available to all populations. Almost overnight a so-called primitive society can experience the boon of civilisation. Sociological revolution has replaced sociological evolution. But as Richard Titmuss [4] puts it:

> " We are beginning to learn, from the advances in knowledge slowly won by the behavioural sciences, that there are limits, particularly in relation to child-rearing practices and family adjustment, to the speed at which social change can take place without causing grave psychological problems. The critical importance to the health of societies of the ways in which new generations of children are socialized within their own families is better understood in the West than it was 100 years ago. We now know that what is passed on through the family—the central mechanism for the transmission of culture—cannot be rapidly changed."

Today's social pathology reflects the ever-increasing gap and time lag between a society's culture and its adaptation to technological advances. Cultural adaptation still follows the biological time-clock, whilst applied science can change the face of the globe in a few short years, or obliterate it in a fraction of a second. There is no evidence to suggest this gap will close or the time-lag shorten. All pointers indicate the opposite: the practical applications of science to daily life will increase exponentially, whilst cultural adaptation to change will maintain its age-old rate. The manifestations of social pathology will increase, not lessen. There will be more and more reason to consider the past as " the good old days ", to enjoy the present, and to view the future with misgivings.

" Clinically " today's social pathology will be manifest in the reactions of the members of society to the increasing perplexities and complexities of life in an industrialised civilisation. Until recently, social factors were not considered to play a significant part in disease causation. An appreciation of the importance of social factors in disease causation was first manifest in social reformers, and then given practical expression by our legislators. Social legislation relating to mental disease, venereal disease, communicable disease, tuberculosis, have been on the statute books of many countries for a considerable time. Legislation to control water supplies, overcrowding, hours of work, conditions of work, food products, &c., indicate an appreciation of the interaction of social and environmental factors with disease states. Much of this legislation antedated the importance of microorganisms or the presence of tissue pathology as the causes and manifestations of disease. Legislation of this type, and the advances of medical science, have had highly beneficial effects on human morbidity and life expectancy. But there remains a great mass of human suffering that shows no signs of diminishing. In spite of improved medical techniques, raised living standards, and more health and welfare legislation, an apparent irreducible mass of sickness remains—minor illnesses, industrial absenteeism, accidents, stress diseases, and the human miseries attendant upon disruption of house, home, and family.

Statistics from several industrialised countries substantiate the existence of a constant mass of ill-defined sickness. There seems little doubt that our social pathology is one of the sources of this ill health. Its lack of response to current medical practice and therapy would suggest the desirability of change in traditional attitude towards disease and its causation. A realisation that disease does not always exhibit cellular or biochemical abnormalities is perhaps overdue.

Changing Concepts of Disease Causation

These interactions between parents, between parents and their offspring, between wage-earners and the work-place, between the work-place and the home lead to a vicious circle in which the internal and personal factors come into conflict with the external and impersonal. Frequently these environmental conflicts become manifest in symptom complexes reflecting individual maladaptation, maladjustment, and stress. These feelings of ill health cannot be accounted for by the germ theory of disease causation. Their lesion or lesions cannot be demonstrated under the pathologist's microscope. Even the biochemist cannot account for it. It may seem strange that this irreducible mass of dis-ease does not exist by the criteria and techniques used today for the detection of disease. The reason, of course, is obvious. Disease is no longer the simple cause-and-effect phenomenon it was hoped to be at the turn of the century.

Feelings of dis-ease are not dependent only on tissue change, germ intrusion, or biochemical abnormality! " The physician is beginning to realise that in the diagnosis of any illness, it is essential to include both physiological and psychological methods against the background

3. Married Women Working for Pay. Department of Labour, Ottawa, 1958.
4. Titmuss, R. M. Essays on the Welfare State. London, 1958.

of the cultural environmental group with which the patient is struggling." [5]

Trends in Medical Education

Concepts of disease are beginning to change. The curricula of medical schools are beginning to reflect an appreciation of the changing pattern of disease and disease causation. Moreover, whereas in 1900 three out of five entering the health field in the U.S. did so as doctors of medicine, by 1950 only one out of five in the field of health was a doctor of medicine.

This trend will continue. Inevitably as our health services expand, the proportion of non-medical personnel will increase. This does not represent a "population explosion" amongst administrators. It reflects the optimal use of trained professionals for the health needs of the nation. The decline in communicable disease, the decrease in acute somatic disease, the increase in degenerative and chronic disease, and the rise in mental disease necessitate the redistribution of health personnel.

This "dilution" of the medical profession with non-medical specialists is not new. The nurse-technician-doctor team is now the normal. Collaboration on a basis of equality with non-medical scientists is accepted as the means to achieve the best in technical competence. No modern teaching university hospital could function without the presence of chemists, physicists, engineers, statisticians, and the like as members of its staff. Such individuals are essential if the science of medicine is to progress.

Further dilution will occur as the medical profession becomes more and more aware of the factors, other than organic disease processes, that contribute to feelings of ill health. Non-medical professionals with training based on knowledge gained from the behavioural sciences will collaborate more with the medical professionals in the health field. Their numbers and their importance will grow as the role of psychosocial-economic factors in disease causation becomes more widely accepted. With the recognition of the role such factors play in disease, these practitioners of applied behavioural science will contribute more to the education and training of health personnel. The blending of the behavioural and natural sciences will result in a broadening of medical horizons, and a change in the traditional doctor-patient relationship. More, rather than less, attention will be paid to the "personal" problems of the patient. This attention will be based not so much on the "art" of medicine or the "intuition" of the doctor as on knowledge and understanding gained from the fusion of the medical with the behaviour sciences.

Conclusion

"When we look at the task that modern society has placed in the hands of its physician, we soon find that the scope of medicine has broadened tremendously. From private relationships between two individuals, medicine is rapidly becoming a social institution. It is one link in a great chain of social welfare institutions. Medicine, usually regarded as a natural science, actually is a social science because its goal is social. Its primary target must be to keep individuals adjusted to their environment as useful members of society, or readjust them when they have dropped out as a result of illness. In combating disease the physician uses methods of natural sciences every day, but to a social end." [6]

5. Dunbar, F. Synopsis of Psychosomatic Diagnosis and Treatment. St. Louis, 1948.
6. Sigerist, H. E. On the Sociology of Medicine. New York, 1960.

CYTOGENETIC STUDIES IN PRIMARY AMENORRHŒA

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A NUMBER of sex-chromosome abnormalities in women are associated with primary amenorrhœa. This is true of the majority of phenotypic females with an XO sex-chromosome complement (Ford et al. 1959), and is also true of all examples so far reported of mosaicism of the XO/XX (Ford 1960) and XO/XXX types (Jacobs et al. 1960). Not only have abnormalities of the number of sex chromosomes been reported in primary amenorrhœa but also morphological abnormalities of one X chromosome. Thus a case reported by Jacobs et al. (1960) had a deletion of an X chromosome, and Fraccaro et al. (1960) have reported three cases with an abnormally large X chromosome. Finally in two conditions abnormal sex differentiation has led to the development of a female phenotype, despite the fact that in each a normal male sex-chromosome complement is present. These conditions of sex reversal are testicular feminisation (Jacobs et al. 1959), and those cases of pure gonadal dysgenesis which are chromatin-negative (Harnden and Stewart 1959).

The findings here reported are from a survey to determine the frequency of sex-chromosome abnormalities and of examples of sex reversal in a group of women who had never menstruated spontaneously.

The Study Population

A list was compiled of all the women referred to one of us (T. N. M.) between Jan. 1, 1946, and Jan. 1, 1960, with a presumptive diagnosis of primary amenorrhœa. Altogether there were sixty-eight, of whom nineteen were eventually shown to have no more than a delayed menarche. In a further five instances an associated disease was regarded as a reasonable explanation for the failure to menstruate. Thus four patients had a chronic inflammatory condition of the pelvic organs, including three with tuberculous endometritis and one who was shown at operation to have adrenal virilism due to simple adrenal cortical hyperplasia. The remaining forty-four patients, therefore, constituted a group in whom failure to menstruate might, in some cases, be due to genetic factors, including chromosome aberrations.

Many of the forty-four patients had ceased to attend the clinic, and we tried to trace and interview all of these. Two patients could not be traced, however, two had died, two were unwilling to be examined, and six had moved out of the area. Sex-chromatin analyses and chromosome studies were, therefore, performed on thirty-two women.

TABLE I—DATA ON 32 PATIENTS AVAILABLE FOR STUDY

Case no.	Height (ft. in.)	Age at examination (yr.)	Parental age at birth (yr.)		Sex-chromosome complement	Summary of clinical features
			Father	Mother		
1	4 6	22	46	36	XO	Sexual hypoplasia. Neck webbing. " Streak " gonads
2	4 6	26	48	35	XO/XY	" " " Streak " gonads
3	4 6	31	27	28	XO	" " No laparotomy
4	4 6	35	38	36	XO/XX	" " " Streak " gonads. Dorsal kyphoscoliosis
5	4 6	30	31	35	XX	" " No laparotomy
6	4 7	27	33	36	XO	" " Neck webbing. No laparotomy
7	4 7	27	25	26	XO	" " " Streak " gonads
8	4 9	28	?	?	XO	" " Neck webbing. No laparotomy
9	4 9	34	25	21	XO/XXX	" " " Streak " gonads
10	4 9	36	37	37	XX	" " No laparotomy
11	4 10	23	35	26	XO	" " Neck webbing. No laparotomy
12	4 10	33	30	27	XO/XYY	" " Neck webbing. No laparotomy
13	4 10	30	27	30	XO/XY	" " " Streak " gonads
14	4 10	24	46	39	XX	" " Bilateral small polycystic ovaries
15	5 1	37	28	23	XX	" " " Streak " gonads
16	5 1	30	33	31	XX	Adult breasts and genitalia. No laparotomy
17	5 1	21	?	?	XX	Adult breasts and genitalia. Bilateral small polycystic ovaries
18	5 1	37	26	28	XX	Sexual hypoplasia. " Streak " gonads
19	5 1	21	34	32	XX	Status before hormone therapy unknown. Diabetes at 6 years. Cystic left ovary
20	5 2	29	?	?	XX	Adult breasts and genitalia. Absent right ovary and fallopian tube
21	5 2	20	44	32	XX	No breast development. Adult genitalia. Bilateral small polycystic ovaries
22	5 2	28	38	36	XX	Sexual hypoplasia. No laparotomy
23	5 2	28	32	35	XX	Adult breast development. Absent vagina and uterus
24	5 3	40	?	20	XX	Sexual hypoplasia. No laparotomy
25	5 3	24	25	25	XX	Adult breast development. Absent vagina and uterus
26	5 4	31	29	25	XX	Sexual hypoplasia. Ovaries unusually small with thickened capsules
27	5 5	21	53	45	XX	Sexual hypoplasia. No laparotomy
28	5 6	22	28	28	XY	Poor breast development. Infantile genitalia. No upper third vagina
29	5 6	31	33	29	XX	Adult breasts and genitalia. Bilateral polycystic ovaries
30	5 7	25	27	27	XY	Slight breast development. Infantile genitalia. No upper third vagina
31	5 8	35	23	23	XX	Status before hormone therapy unknown. Bilateral small polycystic ovaries
32	5 9	27	32	34	XX	Sexual hypoplasia. Absent uterus. " Streak " gonads

These patients are listed in table I, and those not examined in table II.

Techniques

The buccal smears were examined for sex chromatin by one of us (N. M.), using the staining technique described by Ross (1960).

Bone-marrow chromosomes were studied by the technique of Ford et al. (1958), those of the leucocyte component of the blood by a modification of the technique of Moorhead et al. (1960), and skin preparations were made as described by Harnden (1960).

Results and Discussion

Altogether fifteen patients were found to have an abnormal chromosome constitution, and in two more the constitution was that of a normal male. Six patients appeared to have a simple XO sex-chromosome complement (cases 1, 3, 6-8, and 11), and five were found to be sex-chromosome mosaics (cases 2, 4, 9, 12, and 13). In each of these five patients one of the stem-lines present had an XO complement. Case 16 was also a mosaic, but here the sex chromosomes do not seem to be involved. In each of three other patients (cases 5, 10, and 15) there were two X chromosomes, but one of these was morphologically abnormal. All the remaining patients studied, except cases 28 and 30 which had a male sex-chromosome complement, proved to have chromosomes indistinguishable from those of normal females.

The chromosome-count distributions of the abnormal patients are shown in table III,* and the results of the analyses of buccal smears for sex chromatin, and of segmented polymorphs for female appendages are shown in table IV. Examples of the sex-chromatin bodies and the corresponding sex-chromosome complements, as found in the study population, are shown in fig. 1; the sex-chromatin bodies illustrated are examples of the largest bodies seen in each of the relevant patients. We cannot show the mean size, but the variation in size of the largest bodies gives a valid visual impression of the variation in the mean. In the diagrammatic representation the size of the sex-chromatin body is, in each case, somewhat exaggerated. As far as variation in the size of the body is concerned, an indication that the size may be abnormal is only gained after examination of many cells. That such impressions may prove valid is emphasised by the fact that comment on the size of the sex-chromatin body in cases 5, 10, and 15 was made before we knew the chromosome constitution. In no other case in the study population, except case 8, was the size of the body thought to be outside the range of normal.

Data are given in table I which provide some assessment of the status of sexual development of the patient when first seen. Many cases are said to show " sexual hypoplasia ", by which is implied a state of development of the breasts and genitalia which may not differ much from the infantile state. The term " streak gonads " refers to the finding of a thin ridge of tissue in each mesosalpinx in the region normally occupied by the ovary. This primitive structure is composed of fibrous

* In the interests of space, the count distributions of the normal patients are not shown. They will be supplied on request.

TABLE II—DATA ON 12 PATIENTS UNAVAILABLE FOR STUDY

Case no.	Height (ft. in.)	Year of birth	Summary of clinical features
33	4 4	1922	Sexual hypoplasia. Aortic stenosis. No laparotomy. Died 1956—cardiac failure
34	5 0	1931	Sexual hypoplasia. Right ovary palpable. No laparotomy
35	5 1	1924	Adult breasts and genitalia. Uterus and ovaries palpable. No laparotomy
36	5 2	1924	Some breast development. Adult genitalia. No laparotomy
37	5 3	1939	Adult breasts and vulva. Rudimentary vagina. Uterus not palpable. No laparotomy
38	5 3	1918	Vagina <2 in. long. No other data available (sister of case 42)
39	5 3	1930	Sexual hypoplasia. No laparotomy
40	5 4	1920	" " " Streak " gonads
41	5 4	1933	" " No laparotomy
42	5 5	1919	No cervix, and uterus not palpable. No other data available (sister of case 38). Died 1959—accidental death
43	5 5	1931	Adult breasts. No vagina. Uterus not palpable. No laparotomy
44	5 6	1932	Adult breasts and genitalia. Uterus palpable. No laparotomy

TABLE III—CHROMOSOME-COUNT DISTRIBUTIONS OF ABNORMAL CASES

Case no.	Tissue	Date	<44	44	45	46	47	>47	Total	Sex chromosomes	Remarks
1	Marrow	April 15, 1959	1	1	38	..	1	..	41	XO	None
2	Blood	Aug. 19, 1960	..	..	16	82	1	1	100	XO/XY	15 45-cells consistent with XO constitution
	Skin	,,	1	2	44	3	..	..	50		All 3 46-cells consistent with XY constitution
3	Blood	Aug. 22, 1960	2	6	42	1	..	..	51	XO	None
4	Blood	Sept. 12, 1960	..	1	11	86	2	..	100	XO/XX	10 45-cells consistent with XO constitution
	Skin	,,	..	1	2	32	..	..	35		Neither 45-cell consistent with XO constitution
5	Blood	Jan. 1, 1961	..	1	1	30	1	..	33	X_{Δ}	Deletion of short arm of 1 X chromosome
	Skin	,,	2	..	1	28	..	..	31		
6	Marrow	Nov. 17, 1961	..	1	12	..	..	..	13	XO	None
7	Blood	Aug. 13, 1960	..	..	31	..	..	..	31	XO	None
8	Blood	Aug. 16, 1960	1	4	44	1	..	..	50	XO	None
	Skin	,,	..	2	28	..	..	..	30		
9	Blood	Aug. 8, 1960	..	5	88	2	5	..	100	XO/XXX	46-cells in blood and skin consistent with XX constitution (see text)
	Skin	,,	3	3	42	2	14	..	65		
10	Blood	Jan. 3, 1961	..	1	1	35	..	..	37	XX	Enlarged X chromosome, presumed isochromosome
	Skin	,,	..	1	..	29	..	..	30		
11	Blood	Mar. 15, 1960	7	..	21	2	..	..	30	XO	None
12	Blood	Jan. 19, 1961	..	2	69	4	25	..	100	XO/XYY	3 46-cells consistent with XY constitution
	Skin	,,	1	2	60	..	1	..	64		47-cell has XYY constitution
13	Blood	Aug. 12, 1960	..	..	14	86	..	..	100	XO/XY	13 45-cells consistent with XO constitution
	Skin	,,	1	2	27	..	..	..	30		None
15	Marrow	Nov. 3, 1959	2	1	1	21	..	..	25	X^{x}	Data reported by Jacobs et al. (1960)
	Blood	Jan. 19, 1960	3	2	7	87	4	..	103		
	Skin	Jan. 9, 1960	..	2	4	18	..	..	24		
	Skin	,,	..	4	2	26	2	..	34		Deletion of long arm of an X chromosome
	L. gonad	,,	..	2	2	11	..	..	15		
	R. gonad	,,	..	..	2	11	..	..	13		
16	Blood	Sept. 6, 1960	..	..	1	28	1	..	30	XX	None
	Blood	Jan. 21, 1961	..	..	..	30	..	..	30		
	Skin	Sept. 6, 1960	..	..	1	18	9	..	28		The 47-cells are considered trisomic for autosome 10 or 11
	Skin	,,	..	1	3	24	6	..	34		
	Skin	Jan. 21, 1961	..	1	..	11	18	..	30		
28	Blood	Oct. 1, 1960	..	..	..	36	1	..	37	XY	None
	Skin	,,	..	..	1	28	..	1	30		
30	Marrow	June, 5, 1959	..	..	..	14	..	..	14	XY	None

stroma resembling ovarian stroma in which follicles may occasionally be found. The association of sexual hypoplasia, "streak" gonads, and short stature strongly indicates that a chromosome abnormality is present. Thirteen out of fourteen patients, who were 4 ft. 10 in. tall or less, had sex-chromosome abnormalities. The other eighteen patients were 5 ft. 1 in. or more tall, and only two showed a chromosome abnormality (cases 15 and 16), one of which was an autosomal abnormality. The two patients with testicular feminisation (cases 28 and 30) were respectively 5 ft. 6 in. and 5 ft. 7 in.

The results from one of the six patients with an XO sex-chromosome complement require comment, because case 8 shows discrepancy between the sex-chromatin findings and the chromosome analysis. Sex-chromatin studies revealed that 27% of the cells in the buccal smears had a sex-chromatin body, and that this was unusually small (fig. 1*b*). Chromosome analysis revealed a karyotype entirely consistent with an XO constitution, and no autosome abnormality could be seen. If it is accepted that the presence of a sex-chromatin body indicates more material than is carried on a normal X chromosome, then in this case additional X-chromosome material seems to be present. This could be explained by postulating a small duplication on the single X chromosome or the translocation of some X-chromosome material on to an autosome, the abnormality in either case being too small to be detected by present techniques.

THE CHROMOSOME MOSAICS

XO/XY Mosaicism

Cases 2 and 13 are examples of phenotypic females with an XO/XY sex-chromosome constitution. In each the majority of cells from the blood-cultures had an XY complement, although some XO cells were present. In case 13 the cells from the skin-culture showed only an XO stem-line, while in case 2 only 3 out of 50 cells could be regarded as having an XY complement. Clinically both patients had morphologically normal but underdeveloped genitalia, and in both laparotomy revealed "streak" gonads. Biopsy material from these gonads showed, in case 2, some ovarian stroma but no follicles, and, in case 13, mainly connective tissue although in the right gonad there was a cluster of theca-like cells. Neither case had evidence of testicular tissue.

XO/XYY Mosaicism

In case 12 the blood-culture studies revealed both an XO and an XYY stem-line. The 6 small acrocentric chromosomes in these cells were easily paired, and one pair showed the characteristic appearances of the Y chromosome. The study of cells from skin-culture, however, showed that the XO

TABLE IV—NUCLEAR SEX IN THE ABNORMAL CASES

Case no.	Sex-chromatin* analysis			Female nuclear appendages per 500 segmented polymorphs		Sex-chromosome complement	Remarks
	0	1	2	Type A—drumsticks	Type B—sessile		
1	100	0	0	..	..	XO	None
2	100	0	0	0	0	XO/XY	None
3	100	0	0	0	0	XO	None
4	59	41	0	38	7	XO/XX	None
5	70	30	..	18	3	X_{Δ}	Sex-chromatin bodies smaller than normal
6	100	0	0	0	0	XO	None
7	100	0	0	..	..	XO	None
8	73	27	..	0	0	XO	Sex-chromatin bodies very small
9	?	?	?	0	0	XO/XXX	Buccal smears poor. 15/50 cells with sex chromatin had 2 bodies
10	40	60	0	109	22	XX	Many sex-chromatin bodies (about 30%) and drumsticks abnormally large
11	100	0	0	0	0	XO	None
12	100	0	0	..	..	XO/XYY	None
13	100	0	0	0	0	XO/XY	None
15	93	7	0	0	0	X^{x}	Sex-chromatin bodies small
16	58	42	0	25	1	XX	Autosomal mosaic
28	100	0	0	..	..	XY	None
30	100	0	0	..	..	XY	None

* Expressed as % cells in buccal smear with 0, 1, and 2 sex-chromatin bodies.

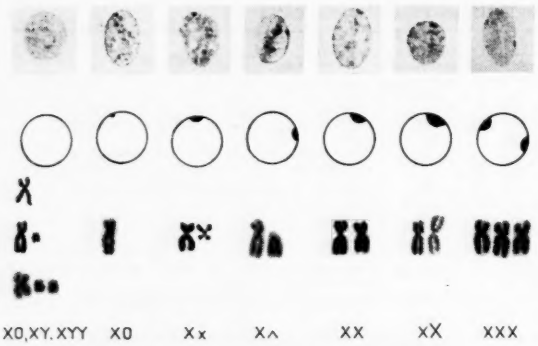

Fig. 1—Sex chromatin and sex chromosomes.

stem-line greatly predominated because only 1 cell in 64 studied had an XYY constitution. On blood-culture 4 cells had a count of 46, and 3 of these on analysis appeared to be normal male cells. While this patient is recorded as an XO/XYY mosaic, the possibility of XO/XY/XYY mosaicism cannot be excluded. The patient is short in stature and has pronounced webbing of the neck. When first seen at the age of 20 she had normal but underdeveloped female genitalia. Laparotomy has not been done.

XO/XX Mosaicism

The diagnosis of mosaicism in case 4 rests solely on the findings from blood-culture, those from skin-culture showing evidence for one stem-line only—that of normal female cells. In the blood-culture the difference between the observed and expected numbers of modal and non-modal cells is statistically significant ($\chi^2 = 7{\cdot}5$, $0{\cdot}001 < P < 0{\cdot}01$, assuming an average of 93% modal cells in preparations made by drying in air). Moreover analysis of the 11 cells with a count of 45 showed that 10 were consistent with an XO complement. We should have liked to study this patient further, but this was not possible. It seems reasonable, however, to accept the patient as an XO/XX mosaic.

XO/XXX Mosaicism

Case 9 represents a different type of mosaicism. The majority of blood-cells had an XO constitution, while all 5 cells with a count of 47 had an XXX constitution. In the 2 blood-cells with a count of 46, the findings were consistent with these being XX cells. The majority of cells from the culture of the skin also had an XO constitution, but compared with the blood findings, a proportionately greater representation of cells had an XXX complement. Again only 2 cells with 46 chromosomes were found, but these were compatible with those of a normal female. Thus while this patient is recorded as an XO/XXX mosaic, the possibility must be borne in mind of her being a triple stem-line mosaic of an XO/XX/XXX constitution. The clinical findings in case 9 differ in a number of respects from those in the original example of XO/XXX mosaicism reported by Jacobs et al. (1960). The present patient was 4 ft. 9 in. tall, with an arm span of 4 ft. 10 in. The earlier patient was 5 ft. 1 in. tall, with an arm span of 5 ft. 7 in., and, unlike case 9, she had unusually masculine proportions, particularly in her shoulder-girdle. The present patient had normal though hypoplastic genitalia, but the previous patient had no vagina.

A 46/47 Mosaic

Case 16 poses an interesting problem. Chromosome studies on cells from blood-cultures showed no abnormality, the karyotype being indistinguishable from that of a normal female. But chromosome studies on three separate skin-cultures from two biopsies revealed evidence for two separate stem-lines—one of normal female cells and the other a line of cells with 47 chromosomes. The additional chromosome in this stem-line is a medium-sized submetacentric chromosome, comparable in size to those of autosome pairs 10 and 11 (fig. 2). Studies of sex chromatin in the buccal smear showed a single sex-chromatin body in 42% of cells, a finding compatible with a normal XX sex-chromosome complement. Buccal smears were made on three separate occasions, and at no time was any cell with two sex-chromatin bodies seen, as would be expected in cells with 3 X chromosomes. Sex-chromatin studies were also done several times on cells from the skin-cultures, and again these were normal chromatin-positive. Similar studies on cells from cultures of skin from women with an XXX sex-chromosome complement have always shown two sex-chromatin bodies in a proportion of cells.

The diagnosis of X-chromosome abnormalities depends on taking in conjunction the chromosome findings and the sex-chromatin studies. This is because the X chromosome is virtually indistinguishable from the larger medium-sized submetacentric autosomes, and because it is reliably established that abnormalities of the number of X chromosomes are reflected in changes in the number of sex-chromatin bodies.

Applying these principles in case 16 leads to the conclusion that the most likely explanation for the additional chromosome is that it is an autosome. The patient is therefore a mosaic containing two stem-lines, one being a normal diploid female line, and the other a stem-line apparently composed of cells trisomic for an autosome, either no. 10 or 11. The patient is 5 ft. 1 in. tall and when first seen at the age of 19 she had normal breasts and genitalia. A number of developmental abnormalities are present, and further investigations are in progress.

General Comment on the Mosaics

It has become apparent from published reports and, from our data, that an appreciable proportion of individuals with sex-chromosome abnormalities are mosaics. It is also apparent that in mosaics the degree of admixture of the component stem-lines may vary widely between tissues.

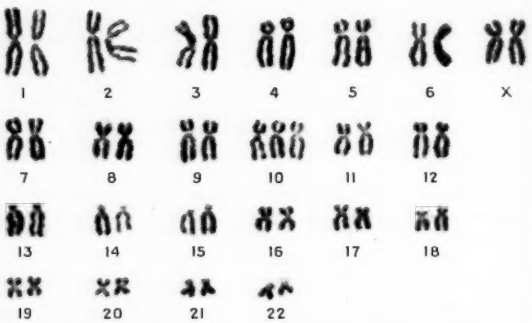

Fig. 2—Case 16: karyotype of cell with 47 chromosomes.

Thus, in case 2, 82% of cells from blood-culture had an XY sex-chromosome complement, while, on the evidence available, 6% at the most of cells from skin-culture might have had an XY constitution. In case 13, another example of XO/XY mosaicism, no cells were noted on skin-culture to have a count of 46 chromosomes, while 86% of the blood-cells had a normal XY sex-chromosome complement. This variability is again emphasised in case 12; in the blood 25% of the cells had a count of 47, and on analysis a chromosomal sex of XYY, whereas in the skin only about 1% had such a constitution. If chromosome studies had been made for these three patients on skin-cultures alone, the mosaic constitution would not have been recognised in cases 12 and 13, and probably not in case 2. Conversely, chromosome studies confined to blood-cultures would have resulted in the mosaicism of case 16 being overlooked.

It follows from these observations that, in cases of suspected sex-chromosome abnormality, chromosome studies ought to be done on two or more different tissues

to gain a realistic evaluation of the frequency of mosaicism. This is, of course, not always possible, as in a number of our patients; and, for example, we cannot be certain that any of our six cases reported to have an XO complement were not in fact mosaics.

Another consideration in mosaicism is the possibility that the sexual phenotype will depend on the relative proportion of the stem-lines in the primitive gonads. This is emphasised by consideration of the clinical data on the two examples of XO/XY mosaicism in this report in relation to clinical reports on other examples of this type of mosaicism. Hirschhorn et al. (1960a) have described an infant with an XO/XY constitution, who showed evidence of masculinisation, with an enlarged phallus and with labia resembling scrotal folds. Both male and female elements were present in each gonad. Miller also (see Hirschhorn et al. 1960b) has found two examples of true hermaphroditism with an XO/XY constitution. By contrast our two patients showed no evidence either of masculinisation or of male elements in their gonads.

It seems reasonable to suppose that the sexual phenotype will be dependent upon the predominant stem-line in the primitive gonads, and in cases 2 and 13 that this was the XO line. In the published cases cited above, there was presumably a significant representation of cells with an XY complement in the primitive gonads. From these arguments, therefore, culture of gonad tissue where possible in sex-chromosome mosaics may materially help in understanding the mechanisms of expression of the sexual phenotype. Finally, if the gonads in a mosaic are completely or almost completely composed of a normal line of cells—either male or female—then it is possible that the sexual phenotype, and even the sexual function, will be normal.

MORPHOLOGICAL ABNORMALITIES OF THE X CHROMOSOME

Morphological abnormalities of the X chromosomes could arise either before or after fertilisation. If they arise after fertilisation, then mosaics could be formed. So far, however, no case has yet been described of a chromosome mosaic whose stem-lines differed only in the morphology of the chromosomes. In the three cases with morphological abnormalities of the X chromosome described here, there is no evidence to suggest that any one is a mosaic; consequently the error leading to the abnormal chromosome must be presumed to have arisen in the parents either during gametogenesis or at some stage before it. But it could be argued that the abnormality arose during an early stage of embryogenesis, though only one cell-line was included in the embryo.

Although structural rearrangements of the chromosomes could occur at any division, they are probably most frequent during meiosis when "crossing over" (which normally involves breakage and rejoining of chromatids and the exchange of material between homologous chromosomes) is occurring; this may be especially likely to happen if previous small rearrangement interfere with the pairing of the homologous chromosomes. All structural rearrangements necessitate at least two breaks in the chromosomes and the subsequent incorrect reunion of the broken ends. If this rejoining causes the elimination of a segment of one chromosome, a deletion is said to have occurred (fig. 3*a*); when the deletion is large, one of the arms of the chromosome will be detectably smaller.

A deletion is the most reasonable interpretation of the findings in cases 5 and 15. In case 5 a normal chromosome-count was found in cells from skin and blood cultures. On analysis, however, an additional large acrocentric chromosome was present, while a chromosome was missing from the range in which the X chromosome is found. The large acrocentric chromosome was similar in general appearance to autosomes 13, 14, and 15, but no satellites were found on the short arms as there are on autosomes 13 and 14. Furthermore the sex-chromatin bodies in cells of the buccal smear appeared smaller than normal (fig. 1*d*). Considering in conjunction all the relevant data, including the clinical findings, the most reasonable interpretation is that the additional large acrocentric chromosome is an X chromosome from which most of the material of the short arms has been deleted.

The data on case 15 have previously been reported by Jacobs et al. (1960), and it is believed that material has been deleted from the long arm of one of the X chromosomes (fig. 1*c*). Clinically both patients presented with sexual hypoplasia. No laparotomy has been performed on case 5, but case 15 is known to have "streak" gonads.

Examination of cells from cultures of both blood and skin in case 10 showed the chromosome-count to be 46. There was, however, an additional long metacentric chromosome of the same size as autosome 3, while a chromosome was missing from the range in which the X is found. Furthermore the sex-chromatin body was unusually large in about a third of the buccal cells in which it was seen (fig. 1*f*), while very large drumsticks were noted remarkably often, being present in over 20% of the polymorphonuclear leucocytes. Taking all these findings into consideration, it is reasonable to presume the additional large metacentric chromosome to be an abnormally long X chromosome.

There are two possible explanations for the origin of

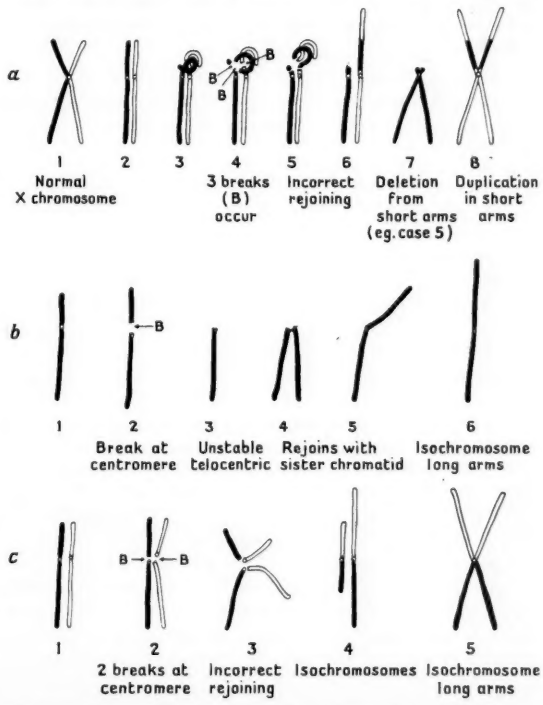

Fig. 3—Modes of origin of morphological abnormalities of X chromosome: (*a*) duplication and deletion, and (*b* and *c*) formation of isochromosomes.

this abnormal chromosome—it may be the result of a duplication, or it may be an isochromosome. Duplication arises when a segment of one chromosome is transferred to its homologous chromosome without reciprocal exchange, so that one segment is now represented twice on the same chromosome (fig. 3*a*). A large duplication will result in one arm appearing longer than normal, and a duplication in the short arms of one X chromosome could produce a chromosome similar in appearance to the abnormal chromosome in case 10. However, this is the fourth such case to be described, three cases having previously been reported by Fraccaro et al. (1960), and it seems unlikely that a duplication would produce an exactly metacentric chromosome on four different occasions. It seems more plausible to suggest that the abnormal chromosome in these cases is an isochromosome, which is a chromosome made up of two homologous arms united at the centromere. This situation can arise either by centric fusion (a special case of translocation [fig. 3*c*]) or by transverse splitting of the centromere instead of the normal longitudinal splitting which precedes anaphase (fig. 3*b*).

Consideration of the stature of cases 5, 10, and 15 is possibly of genetic interest.

The patients were respectively 4 ft. 6 in., 4 ft. 9 in., and 5 ft. 1 in. tall. We regard case 5 as showing a deletion of the short arms of the X chromosome, and case 10 (accepting the isochromosome theory) as monosomic for the short arms and trisomic for the long arms of the X chromosome. Both patients are significantly short in stature, and should be contrasted with case 15, this patient not being unusually short and having a deletion of the long arms. It is also relevant that short stature is a consistent feature of people with an XO complement. Finally, the three patients reported by Fraccaro et al. (1960) as probably having an isochromosome for the long arm of the X chromosome are all short in stature, being respectively 4 ft. 3 in., 4 ft. 4 in., and 4 ft. 7 in. (Dr. M. Fraccaro, personal communication).

It seems possible, therefore, that the study of further comparable cases, may help to determine whether genes which influence height are present on the short arm of the X chromosome.

THE CASES OF SEX REVERSAL

Case 28 was first seen in 1955, when aged 17. At that time her breasts were not fully developed, she had no axillary or pubic hair, and her external genitalia were infantile. The vagina, about 1 in. long, ended in a blind pouch. Laparotomy showed that the uterus was absent although enlarged gonads were present. Histological examination of biopsy material from either gonad revealed immature but otherwise normal testicular tissue. Chromosome analysis showed the patient to have an XY-chromosomal sex, and this taken in conjunction with the clinical data, supports a diagnosis of testicular feminisation. The patient is the only surviving child of a sibship of three, the other two sibs being twin girls who died shortly after birth. Neither paternal nor maternal sibships reveal a history of primary amenorrhœa.

Case 30, first seen in 1955, when aged 20, had little breast development, no axillary hair, scanty pubic hair, and normal development of the vulva. The vagina was about 1·5 in. long, and the cervix was absent. Laparotomy showed absence of the uterus, appendages, and gonads. Chromosome studies showed an XY-chromosomal sex. In November, 1959, bilateral inguinal testes, which were palpable, were excised, confirming the diagnosis of testicular feminisation. This patient is one of a sibship of six, including four sisters. One of these died shortly after birth; the other three menstruate normally. As far as is known the sibships of neither parent have a history of primary amenorrhœa.

FREQUENCY OF ABNORMALITIES IN THE STUDY POPULATION

Altogether fifteen patients were found to have an abnormal chromosome constitution, including fourteen with a sex-chromosome abnormality, and one who, on present evidence, is regarded as an autosomal mosaic. Furthermore there were two examples of sex reversal among the thirty-two patients we were able to study. We do not know whether the autosomal abnormality of case 16 is relevant to her primary amenorrhœa, but for present purposes we assumed it to be so. Of the sixty-eight patients referred with a presumptive diagnosis of primary amenorrhœa, the failure to menstruate spontaneously was associated in at least 25% with abnormalities detectable on cytogenetic analysis. If the nineteen patients with a delayed menarche are excluded, and also those five patients with an associated disease thought to explain the failure to menstruate, then at least 39% of the remaining patients were either cytogenetically abnormal or had a normal male sex-chromosome complement.

A more accurate estimate of the frequency may be obtained, however, by considering the data in table II.

It is most likely that, had it been possible to study case 33, the patient would have been shown to have either an XO constitution, or to have been a mosaic with an XO stem-line. The short stature and the sexual hypoplasia are in keeping with such an assumption. Furthermore, there is good reason for regarding case 37 as an example of testicular feminisation. This patient is one of a sibship of ten girls, two of whom died shortly after birth, five of whom are known to menstruate, and three of whom have primary amenorrhœa. The patient could not be studied further because she had emigrated, but one of her two sisters with primary amenorrhœa proved to have an XY sex-chromosome complement, and inguinal testes were found at operation. Testicular feminisation is thought to be associated with either a sex-linked recessive gene or a sex-limited autosomal dominant gene. Therefore, in view of the family history and the demonstration that one sib was an example of testicular feminisation, it is reasonable to consider case 37 as another example of this condition.

If cases 33 and 37 are added to the number of known abnormalities, and if it is assumed that the study population is a fair sample of patients referred with a presumptive diagnosis of primary amenorrhœa, then in about 28% of such cases a chromosomal abnormality is present. Moreover, if patients with a delayed menarche are excluded, and also those with some associated disease to which the failure to menstruate can be related, then at least 43% of cases with primary amenorrhœa can be explained through cytogenetic study.

Summary

Data are reported on a survey to determine the frequency of sex-chromosome abnormalities, and of sex reversal, in a group of women referred with a presumptive diagnosis of primary amenorrhœa.

The findings indicate that some 28% of such cases can be explained by means of cytogenetic study. If patients are excluded who only have a delayed menarche, or who have some associated disease which adequately explains the failure to menstruate, then the minimal frequency rises to about 43%.

We are grateful to Miss M. Brunton, Miss S. Brunton, Mr. J. Mitchell, and Miss G. Woodcock for technical assistance.

References at foot of next column

FAMILIAL FRUCTOSE AND GALACTOSE INTOLERANCE

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FRUCTOSURIA is a characteristic feature of at least two distinct inborn metabolic diseases. The first is *essential fructosuria*, a symptomless condition which, on routine analysis with Benedict's solution, is sometimes misdiagnosed as diabetes mellitus. The responsible chemical lesion is probably defective phosphorylation of fructose to fructose-1-phosphate (fig. 1) (Hers 1957, Leuthardt 1958), but the defect cannot be demonstrated in red blood-cells and it does not interfere with other metabolic processes (Silver and Reiner 1934, Lasker 1941, Marble 1947, Lenzner 1956). To distinguish the second syndrome from essential fructosuria, it is best called *fructose intolerance* (Froesch et al. 1959). In this condition fructose either by mouth or by injection induces a sharp rise in blood-fructose and a precipitous fall in blood-glucose which may be accompanied by severe gastrointestinal, neurological, and mental symptoms and signs.

In 1956 Chambers and Pratt described briefly a case of "idiosyncrasy to fructose" in a 24-year-old spinster whose only complaints were mild phobic symptoms and attacks of nausea and vomiting after eating food containing fruit or cane-sugar. The attacks were accompanied by a moderately raised blood-fructose and by fructosuria; but no enzyme studies or true-glucose estimations were reported. More recently in a carefully investigated Swiss family the abnormality appears to have been transmitted by an autosomal recessive gene (Froesch et al. 1957, 1959). In affected members the periods of fructosæmia and hypoglycæmia were accompanied by nausea, vomiting, hæmatemesis, trembling, profuse sweating, and somnolence. A boy aged $6^1/_2$ years was mentally retarded, though his mother had discovered when he was 8 months old that the attacks could be prevented by withholding from him sweets, fruits, and carrots. His sister, who had always been on a diet, was normal at $3^1/_2$ years. The clinical and biochemical findings were similar in two cases studied by Wolf et al. (1959) in Germany; but the inheritance in this family—as in the cases to be reported here—may have been through a dominant and perhaps sex-linked gene. Further possible cases are now being investigated on the Continent (de Branlé, 1960).

In no previous case of either essential fructosuria or fructose intolerance has galactose intolerance been reported. Galactose metabolism was normal in the family studied by Froesch et al. (Froesch 1960) and in the patient of Chambers and Pratt (Pratt 1961). Wolf et al. (1959) found a trace of galactose in the urine of one of their patients. We report here a familial case of fructose intolerance associated with galactose intolerance and hypoglycæmia.

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Case-report

A 51-year-old single woman was admitted to Central Middlesex Hospital on Nov. 25, 1959. For about two months her sister had noticed that she had become progressively slower, more irritable, and forgetful; for a month she had complained of intermittent abdominal pain and vomiting; and puffiness of the face and ankles had been noticed. Her speech became slurred; her walking became increasingly unsteady; she had periods of confusion; and eventually she took to her bed and slept most of the time.

Much of her past history was obtained from her sister. Her birth and early development were normal, and her performance at school was average. She was, however, of a nervous disposition, shy and frightened of other children; and she had nocturnal enuresis to the age of 12. She tended to be somewhat clumsy in her movements, described by her sister as "jerky rather than smooth". Aged 13 she started to have epileptic fits which soon became frequent and severe; and she was admitted to an epileptic colony. She remained there till the age of 33 (1941), when she was discharged to live with her sister; and her epilepsy remained fairly well controlled by phenobarbitone and phenytoin sodium. For five years she was able to hold a job as a shop assistant, but in 1946 the fits became more frequent and she had to give up.

In 1948 she was admitted to the mental observation ward of Central Middlesex Hospital in a confusional state, following a series of fits the previous week; and she was noted to have slurred speech, nystagmus, and cerebellar ataxia. Over-dosage of phenytoin sodium was postulated, and with reduction of dosage she seemed to improve.

In 1950 she was admitted to the National Hospital, Queen Square, in a similar condition, again after a series of fits. The cerebrospinal fluid and urine contained an excess of barbiturates, and the cerebellar signs were thought to be due to overdosage. Again she improved after withdrawal of barbiturates. Her sister now tells us that on both of these occasions her condition had gradually deteriorated for a month or two with increasing slowness, irritability, slurring of speech and unsteadiness in walking, puffiness of the face, and periods of confusion. Before her admission to the National Hospital her hair had started to fall out in handfuls so that almost total alopecia developed.

In 1954 she was put on primidone, and she remained free from major fits till the summer of 1959 when she had one attack following reduction of dosage. During this time she was able to hold down a job at a Remploy factory.

At different times she has had a number of food fads, but it was impossible to obtain either from her or from her family a consistent history of distaste for fruit, milk, or any other particular foods. She was, however, always very fond of sweets, sugar, and chocolate, and she ate a lot of potatoes. It may be significant that in the summer of 1959 she decided to go on a diet and cut down on these drastically.

Apart from her major convulsions, all her life she has had minor attacks which she describes as "hot flushes". In these attacks she feels giddy and trembly, her legs become weak, black spots develop in front of her eyes, and sweat pours down her face. She has told us since that symptoms similar to these constitute an aura of her major epileptic fits.

Clinical Examination

The patient lay curled up in bed, mildly confused, uninterested, and slow to answer questions. Her speech was slow, thick and slurred; her face was puffy; her skin was dry; her eyebrows were scanty; and her hair was thin. There was coarse nystagmus to right and left, incoordination, and severe ataxia of the limbs; and she could not walk unaided. Her temperature was 98°F, pulse-rate 80, and blood-pressure 140/80 mm. Hg.

General Investigations

The urine contained no albumin and gave negative reactions on repeated examinations with 'Testape' (glucose oxydase) in the ward. Repeated glucose-tolerance tests and estimations of fasting blood-sugar levels (see accompanying table), blood-urea, serum-cholesterol, serum-calcium, serum-phosphorus, and serum-electrolytes were within the normal range. Liver-function tests were normal (serum-proteins 6·8 g. per 100 ml. with a normal albumin/globulin ratio). The hæmoglobin-level varied between 11·5 and 12·4 g. per 100 ml. White-blood-cell counts and erythrocyte-sedimentation rates were normal. Some blood-films showed a tendency to macrocytosis (mean corpuscular hæmoglobin concentration 30–34%); but the serum-vitamin-B_{12} was 210 µg. per 100 ml. (normal range 140–900 µg.) and folic-acid excretion was normal. Wassermann and Kahn reactions were negative. The cerebrospinal fluid was normal. Myxœdema was excluded by a normal radioactive-iodine excretion; and the urinary 17-ketosteroid excretion was normal.

The electroencephalogram (E.E.G.) in December, 1959, showed a mild and diffuse abnormality: against a wide background of low-voltage fast activity the alpha-rhythm was about 8–9 cycles per second and unstable in frequency. Some random slower components were seen. There was no significant asymmetry, focal abnormality, or paroxysmal behaviour; and no further disturbance resulted from overbreathing or photic stimulation.

Investigations of Carbohydrate Metabolism

In January, 1960, it occurred to us that the patient might be suffering from "masked hypoglycæmia"—a low true blood-glucose masked by a normal total blood-sugar. Repeated examinations of random blood samples showed that her non-glucose sugar-fractions accounted for between a third and half of the total—a higher proportion than is normal (see table).

Response to oral fructose, galactose, leucine, and alcohol.—The table shows the patient's abnormal response to fructose and galactose, given by mouth either neat or mixed with glucose. Test-doses of 10 g. leucine and 10 g. casein (Cochrane et al. 1956) had no ill-effects clinically and caused no significant change in the blood-sugar levels. She had no alcohol intolerance.

An *intravenous fructose-tolerance test* was performed while an E.E.G. was being recorded (fig. 1). During the test the patient passed into a state of hypoglycæmia precoma which responded promptly to intravenous glucose and glucose drinks. On the E.E.G., high-altitude synchronous waves at 4 cycles per second coincided with clinical hypoglycæmia but a high total blood-sugar-level. The serum-phosphorus fell from 4·3 mg. to 2·9 mg. per 100 ml. during the first hour and rose again to 4·4 mg. after another two hours. During the first hour the lymphocyte-count rose from 1600 to 6800 per c.mm., without significant changes in the number of polymorphs, eosinophils, basophils, or monocytes.

An *intravenous galactose-tolerance test* also induced mild clinical hypoglycæmia (fig. 2). During the first fifty minutes the serum-phosphorus fell from 4·2 mg. to 4 mg. per 100 ml.

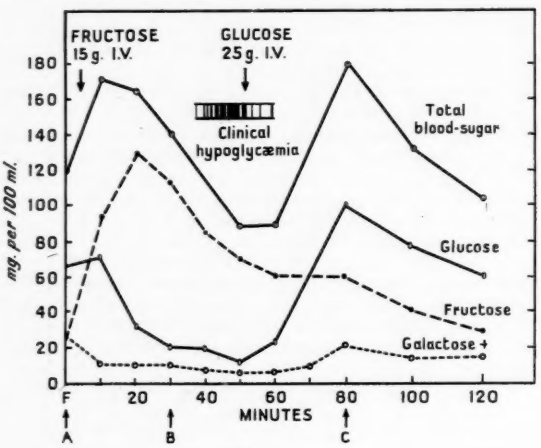
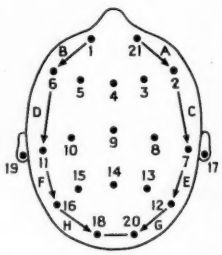


Fig. 1a.



Key to Fig. 1b.

Fig. 1—(a) Changes in the various blood-sugar fractions after intravenous fructose; (b) extracts from the E.E.G. 4, 60, and 90 minutes after the injection.

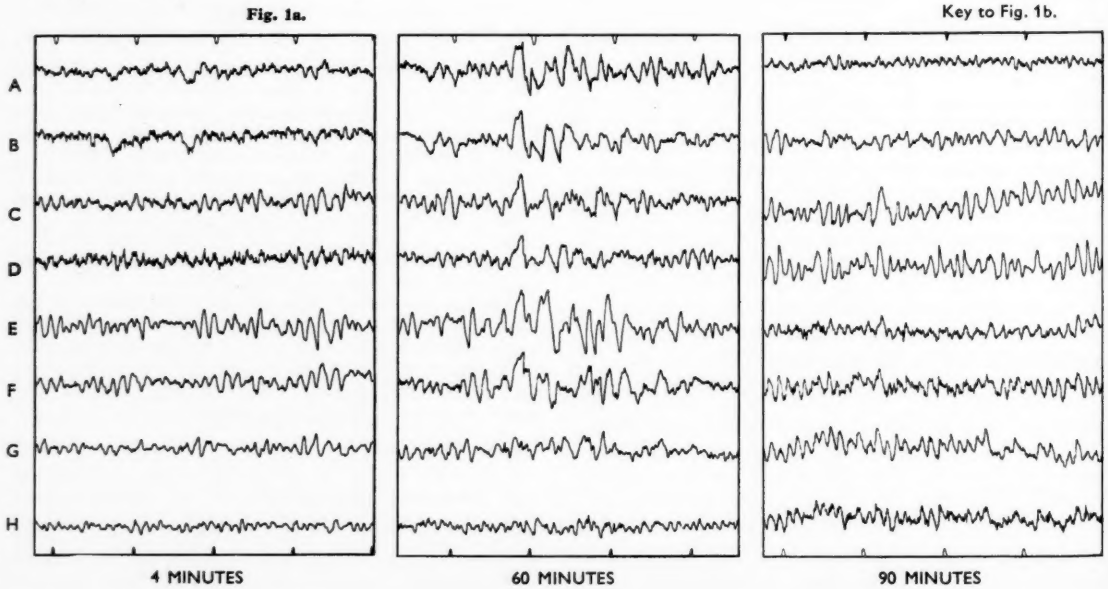


Fig. 1b.

The only significant change in blood-cytology was a rise in the lymphocyte-count from 1500 to 2100 per c.mm.

Forty-eight-hour blood-sugar studies.—The patient's two-hourly total-blood-sugar and blood-glucose levels over a two-day period on an ordinary hospital diet were compared with variations in a normal control. The results are shown in fig. 3.

Urine chromatograms were examined for sugars and amino-acids. All twenty-four-hour samples gave large fructose spots; smaller spots were present for galactose and levan; and on two chromatograms small spots were present for glucose. The corresponding urinary fructose-concentrations varied between 300 and 400 mg. per 100 ml.; the concentration reached

CHANGES IN THE TOTAL-BLOOD-SUGAR (T.B.S.), BLOOD-GLUCOSE (B.GL), BLOOD GALACTOSE (B.GAL), AND BLOOD-FRUCTOSE (B.FR.) LEVELS (mg. per 100 ml.) AFTER VARIOUS COMBINATIONS OF SUGARS TAKEN BY MOUTH

Sugar administered	Estimation	Time (min.)					
		Fasting	30	60	90	120	150
Glucose 50 g.	T.B.S.	98	140	168	160	90	113
	B.Gl.	62	100	128	135	62	72
	B.Gal.	14	20	8	12	6	10
	B.Fr.	22	20	32	13	22	21
Glucose 25 g. + Fructose 25 g.	T.B.S.	108	190	170	124	108	118
	B.Gl.	78	50	35	35	40	58
	B.Gal.	18	10	8	5	10	12
	B.Fr.	12	130	127	84	58	38
Fructose 40 g.	T.B.S.	110	190	212	163	122	115
	B.Gl.	78	50	31	26	35	41
	B.Gal.	10	8	6	4	4	6
	B.Fr.	26	132	177	133	83	70
Glucose 25 g. + Galactose 25 g.	T.B.S.	108	188	164	118	103	114
	B.Gl.	65	70	51	69	73	75
	B.Gal.	15	94	97	31	18	19
	B.Fr.	18	24	16	18	12	20
Galactose 40 g.	T.B.S.	112	206	189	150	118	118
	B.Gl.	68	48	46	51	61	80
	B.Gal.	22	128	113	67	38	15
	B.Fr.	22	30	30	22	19	15

The blood-glucose was estimated by a modification of the method of Middleton and Griffith (1957), the blood-fructose by the method of Roe (1934) and Roe et al. (1949). The blood-galactose is expressed as the difference between the sum of the blood-glucose and blood-fructose and the total blood-sugar as estimated by a modification of the Folin and Wu method.

650 mg. per 100 ml. after the mixed oral glucose-fructose test-dose. In twenty-four samples the urinary galactose varied between 20 and 200 mg. per 100 ml. After the mixed glucose-galactose test-dose the level rose to 350 mg. per 100 ml. Two-way aminoacid chromatograms of twenty-four-hour samples were normal, except for an unusually prominent β-amino-isobutyric-acid spot. A sample collected some hours after the glucose-fructose test-dose showed an increase in the size of the serine, glycine, alanine, cysteine, and threonine spots, as well as the appearance of small spots for valine, proline, hydroxyproline, and an unidentified trace substance. A much smaller increase in the spots and no new spots were given by the urine specimen collected shortly after the mixed glucose-galactose test-dose.

Enzyme-studies.—Heparinised red-blood-cell suspensions were prepared from blood taken from the patient, her sister, a known case of galactosæmia, and normal controls by the method used by Selwyn and Dacie (1954) in their investigations of red-cell metabolism in hæmolytic anæmias. The suspensions were incubated both without added sugar and with various combinations of different sugars. The degree of autohæmolysis suggested that glucose utilisation by galactosæmic red cells, but not by the red cells of our patient and her sister, was inhibited by the presence of galactose. We subsequently estimated uridyl-transferase activity in the red cells of our patient and three normal adults (Schwarz 1958) and found no significant difference. We hope to report later the results of estimations of hexose-phosphates and fructose-1-phosphate levels in the patient's blood.

The Family

Nothing in the parents' medical history suggested metabolic disease; and there was no consanguinity in the family. The

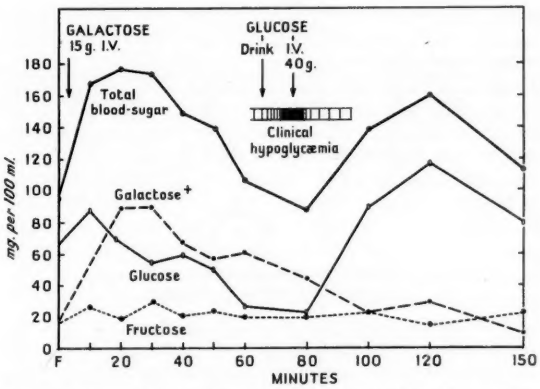


Fig. 2—Changes in the blood-sugar fractions after intravenous galactose.

oldest of eight siblings died in infancy from convulsions; and an elder sister who died in 1958 from hypertensive heart-disease is said to have had "fainting fits" during most of her life (fig. 4). Only one specimen of her daughter's urine was available for chromatographic examination: it showed a trace of fructose but no galactose or glucose. She is said to be normal clinically.

The only surviving sister was clearly affected by the same metabolic abnormality as our patient, but less severely. Apart

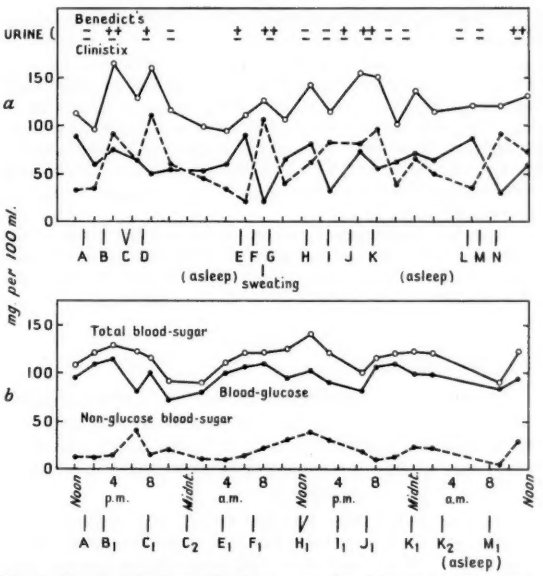


Fig. 3—Forty-eight hour blood-sugar study of (*a*) the patient, and (*b*) a normal control.

A, A_1: Stew, vegetables, "rainbow jelly", milk-pudding, bread and margarine, coffee/tea. B, B_1: Bread and butter, tomatoes, cheese, 2 bananas, chocolate biscuits. C, C_1: Mixed salad, potatoes, 1 egg, dates, orange squash, bread and butter, tea. Bar of chocolate at C only. C_2: Meat sandwiches, $^1/_2$ pint of milk. E, E_1: 2 cups of tea, glucose drink, chocolate biscuits. F, F_1: $^1/_2$ grape-fruit, cornflakes with milk, bread and butter, marmalade, 1 egg, 2 cups of tea. G: Glucose drinks, dry biscuits. H, H_1: Cauliflower cheese, bread and margarine, potatoes, pears and custard, tea. Bar of chocolate at H only. I, I_1: Bread and butter, marmalade, tea, 2 bananas, slice of cake. J, J_1: Brown soup, cheese, ham, bread and butter, ice-cream, tea. K, K_1: 2 cups of tea, chocolate biscuits. K_2: Ham sandwiches, $^1/_2$ pint of milk. M, M_1: $^1/_2$ grape-fruit, bread and butter, marmalade, 1 apple, 2 cups of tea. N: Chocolates. (Unsweetened drinks not indicated.) The patient smoked 8, the control 42, cigarettes in forty-eight hours. All urine specimens of the normal controls gave a negative Benedict's test.

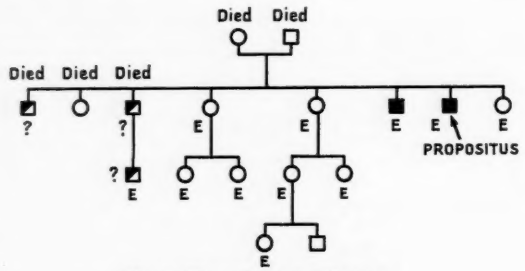


Fig. 4—The patient's family-tree.
E: examined and/or investigated.

from long-standing severe rheumatoid arthritis she was physically and mentally normal. Her specimens of urine contained 0–0·5 g. of reducing substances per 100 ml. Her urinary-sugar chromatograms gave a strikingly similar pattern to those obtained from our patient's urine: fructose, galactose, and glucose spots in that order but all smaller. Her urinary aminoacid pattern was also similar, with a characteristically prominent spot for β-aminoisobutyric acid. (This was also seen on the chromatogram of one of the three healthy brothers.) Fig. 5 shows her response to fructose and galactose by mouth.

The sugar-chromatograms of the three surviving brothers showed no trace of galactose or fructose; and nothing in their or their children's history pointed to metabolic disease.

Progress

A low-fructose, low-galactose diet, supplemented by extra glucose, was devised; and there is no doubt in the patient's or our own minds that she has considerably benefited from it. She soon became more alert and active, and she was discharged on March 30, 1960. Since June, 1960, she has been at work in the Remploy factory, where her friends say that they have never seen her so well. She has not been on anticonvulsants for several months now, and she has had no major fits; occasional mild hypoglycæmic attacks—her "hot flushes"—rapidly subside on taking glucose.

Since her discharge two early-morning and one twenty-four-hour specimen of urine contained 200, 220, and 150 mg. fructose and 100, 120, and 10 mg. galactose per 100 ml. This is a considerable improvement on previous findings.

Discussion

The Metabolic Lesion

The biochemical findings in this patient at first suggested multiple blocks in the metabolic pathways of fructose, galactose, and glucose; but it now seems equally or more likely that all her abnormalities are secondary to a parent defect in fructose metabolism.

Fructose is normally metabolised by way of fructose-1-phosphate to glyceraldehyde and phosphodioxyacetone (fig. 6). The requisite enzymes—fructokinase and 1-phosphofructaldolase—are present in high concentrations in the liver, kidneys, and intestinal mucosa (Hers 1957, Kaletta et al. 1957). Other tissues, notably red blood-cells, contain a non-specific hexokinase which is capable of metabolising fructose in vitro by way of fructose-6-phosphate but which has a far greater affinity for glucose (fig. 6) (Nossal 1948, Widdas 1954). Froesch et al. (1959) have compared in a Warburg apparatus the oxygen uptake of their patient's red cells with that of normal erythrocytes incubated alternatively with glucose or fructose. Both red-cell preparations were capable of using either fructose or glucose as substrates with about equal facility. Our red-cell incubation experiments support their conclusion that patients with fructose-intolerance are not deficient in non-specific hexokinase; but it is unlikely that this enzyme promotes fructose phosphorylation in a glucose-rich milieu.

The underlying enzyme defect in fructose intolerance seems to be a block at the second stage of fructose breakdown along the specific fructose-1-phosphate pathway. The distinct fall in serum-phosphorus after intravenous injection of fructose points to a normal first stage—i.e., phosphorylation of fructose by fructokinase (fig. 6). In the absence of 1-phosphofructaldolase, however, fructose-1-phosphate is not broken down into two three-carbon compounds but accumulates in the cell. Using rat-liver homogenates, Kjerulf-Jensen (1942) and Froesch et al. (1959) have found that fructose-1-phosphate in concentrations of $10^{-2}M$ completely inhibits fructokinase; and even at concentrations of $5 \times 10^{-3}M$ the phosphorylation of fructose is impeded (Schmidt et al. 1958, Froesch et al. 1959). Thus a deficiency of 1-phosphofructaldolase could well account for the fructosæmia; and this seems the more likely explanation since neither in the cases studied in Switzerland nor in our patient and her sister was there any evidence of a block in fructose breakdown beyond the glyceraldehyde stage. One cannot exclude the further possibility that in some cases—perhaps in the patient reported by Chambers and Pratt (1956)—fructose intolerance might be caused by tissue sensitivity to fructose rather than by a metabolic block due to an enzyme deficiency.

At least two mechanisms could account for the hypoglycæmia which accompanies the rise in blood-fructose:

1. A rise in blood-sugar initiates a metabolic and endocrine response which will tend to restore the blood-sugar to the resting level. In healthy adults such a rise is always due to an

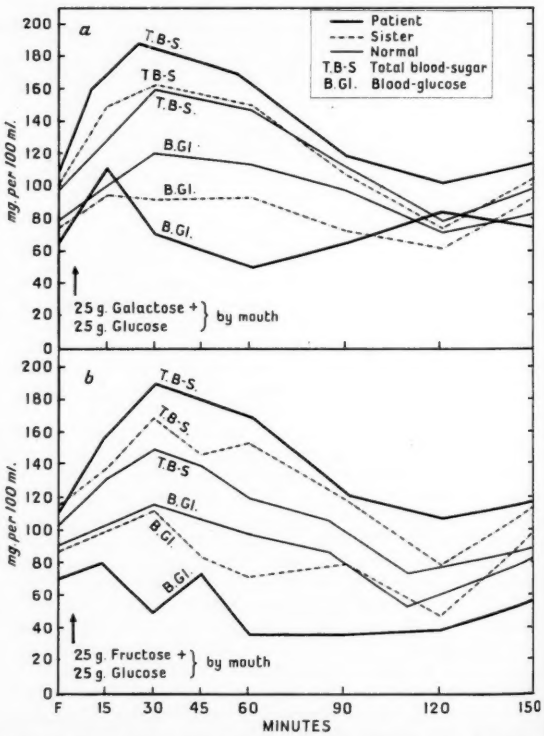


Fig. 5—Changes in the total-blood-sugar and blood-glucose levels in the patient, her sister, and a normal control in response to (*a*) galactose and glucose by mouth, and (*b*) fructose and glucose by mouth.

increase in blood-*glucose*; but it can be shown experimentally that non-glucose sugars will also elicit a homœostatic reaction (Dormandy et al. 1959). Since, moreover, the reaction does not discriminate between the different blood-sugar fractions, a rise in blood-fructose could lead to a reactionary fall in blood-glucose and possibly to hypoglycæmic symptoms.

2. Froesch et al. (1959) have investigated the effects of fructose-1-phosphate on the enzyme system involved in hepatic gluconeogenesis. Their findings so far suggest that, beside its inhibitory effect on fructokinase, fructose-1-phosphate in higher concentrations also inhibits the enzyme 1-6-diphospho-fructaldolase and could thus interfere with the maintenance of the normal blood-glucose level (fig. 6) (Wolf and Leuthardt 1959).

Possibly the two mechanisms are complementary.

Though our patient's galactose intolerance was almost as severe as her fructose intolerance, it always seemed unlikely that she was suffering from the true congenital galactosæmia syndrome. She lacked some of the characteristic clinical stigmata; her galactose-tolerance curve, though abnormal, was not typical; and we were unable to demonstrate in her red blood-cells a specific deficiency of P-gal-uridyl-transferase (fig. 6) (Schwarz et al. 1956, Isselbacher 1957, Hsia 1959). However, the uridyl-transferase system is probably not the only metabolic pathway of galactose in the body (the probable explanation for the spontaneous improvement in the galactose tolerance of galactosæmic children); and it seems likely that the galactose intolerance in our family reflects a block in one of these alternative hepatic pathways. This could be a distinct inborn defect or the result of competitive inhibition by an intermediate metabolite of fructose: either could lead to intracellular accumulation of galactose-1-phosphate. This not only would inhibit the phosphorylation of galactose by galactokinase but also could interfere with hepatic glucolysis by inhibiting the enzyme phosphoglucomutase (fig. 6) (Ginsburgh 1957, Sidbury 1957). Differential estimations of the serum-hexose-phosphates might clarify this point.

Our patient's transient aminoaciduria after oral fructose and galactose probably reflects a non-specific disturbance of renal tubular function by one of their intermediate metabolites. The high concentrations of β-amino-isobutyric acid appears to be a familial characteristic of little significance. Proline and hydroxyproline, however, are normal

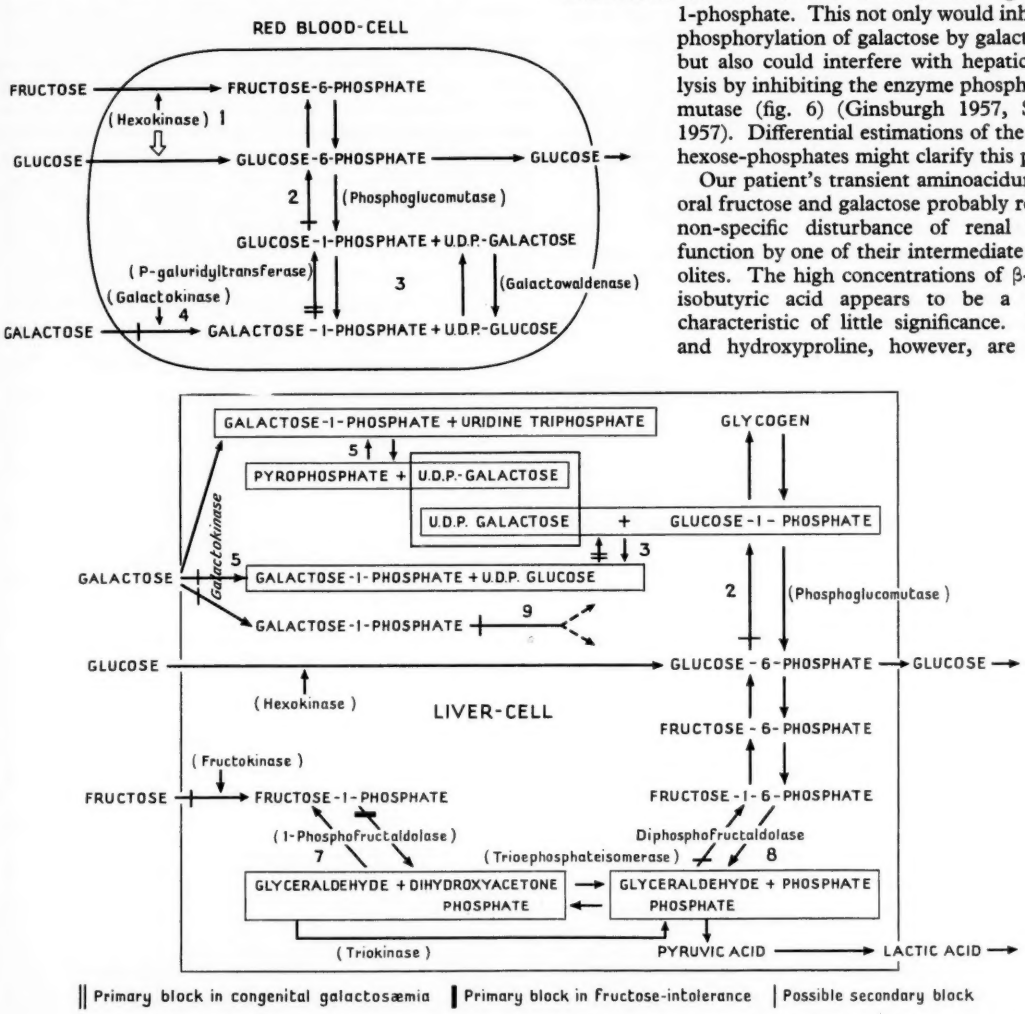


Fig. 6—Some pathways in the conversion of fructose and galactose to glucose in the red blood-cell and liver-cell.

(1) A non-specific hexokinase capable of promoting the phosphorylation of fructose in vitro. (2) Phosphoglucomutase is partially inhibited by high concentrations of galactose-1-phosphate and, probably, of fructose-1-phosphate. (3) P-gal-uridyl-transference is deficient in congenital galactosæmia but not in galactose intolerance. (4) The intracellular accumulation of galactose-1-phosphate inhibits the further phosphorylation of galactose. (5) One of probably several alternative pathways of galactose metabolism. The reaction is catalysed by the enzyme U.D.P.-galactose-pyrophosphorylase (LeLoir 1951, Hsia 1959). (6) A specific fructokinase promotes phosphorylation of fructose in the liver. (7) An inherited deficiency of 1-phosphofructaldolase is the probable metabolic lesion in fructose intolerance. Accumulation of fructose-1-phosphate leads to a rising blood-fructose. (8) Diphosphofructaldolase may also be partly inhibited by high concentrations of fructose-1-phosphate. (9) Other possible hepatic pathways for the conversion of galactose to glucose. One of these may be blocked in galactose intolerance.

urinary trace-constituents only between a few days and a few months after birth (Woolf and Norman 1957, Jagenburg 1959).

Clinical Manifestations

Both clinical and electroencephalographic evidence suggests that acute hypoglycæmic attacks were the patient's main disability. However, though permanent cerebral damage (with a persistently abnormal E.E.G.) is a recognised complication of recurrent hypoglycæmia (Revitch 1954, Shagass and Rowsell 1954, Moorehouse 1956, Sackner and Balian 1960), it seems probable that some of the clinical features—e.g., puffiness, abdominal pain, vomiting—reflected the toxic effects of accumulated intermediate fructose and galactose metabolites.

A tentative clinical diagnosis of hypoglycæmia was wrongly dismissed on several occasions because the patient's total blood-sugar and glucose tolerance were normal. Nervous tissue, however, is unable to metabolise sugars other than glucose and depends for its proper functioning on the body's ability to convert them into glucose or to eliminate them through the kidneys. It is essential, therefore, in suspected cases of intermittent hypoglycæmia to estimate the proportion of the blood-glucose to the total blood-sugar. Though fructose and galactose have practically no renal threshold in normal people, and reducing substances could therefore be expected to appear in the urine with very low blood-levels, it seems possible that a renal threshold develops in patients with long-standing fructose and galactose intolerance (fig. 3).

The cases of Froesch et al. suggest that in fructose intolerance, as in most other inborn metabolic errors, the earlier the diagnosis, the better both the prognosis and the response to a suitable diet (Froesch et al. 1959, Moncrieff 1960). The body can usually reach its metabolic goal by several alternative chemical pathways; and when the main path is blocked, accessory mechanisms may be able to cope with a reduced load. As was shown in our patient's sister, minor degrees of fructose intolerance and galactose intolerance need not interfere with general health; but infants and children are almost certainly more vulnerable than adults and may suffer permanent cerebral damage even though their tolerance later improves.

Summary

A familial case of fructose intolerance and galactose intolerance is described.

This hitherto unrecognised inborn metabolic error closely resembles the recently recognised abnormality of fructose intolerance. Both disorders must be distinguished from symptomless or essential fructosuria.

In patients with fructose intolerance routine blood-sugar estimations may fail to reveal low blood-glucose levels.

We should like to thank Dr. George Discombe for much help, advice, and encouragement. For some of the laboratory investigations and for help with others we are grateful to the departments of hæmatology and biochemistry, Postgraduate Medical School, Hammersmith Hospital, and to Dr. L. I. Woolf (Oxford) of the Medical Research Council. We have received valuable advice from Dr. E. R. Froesch, Zürich; Dr. F. X. de Branlé, Paris; and Dr. C. C. Evans, consultant in electroencephalography at the Central Middlesex Hospital. Mr. Donald Rossington, A.I.M.L.T., and his staff have given us unsparingly of their skill, knowledge, and off-duty time; and, if we have come to take this almost for granted, they have but themselves to blame.

References at foot of next column

INOCULATION OF HUMAN VOLUNTEERS WITH A STRAIN OF VIRUS ISOLATED FROM A COMMON COLD

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WE have recently described the isolation of a virus (strain H.G.P. or Salisbury 1/57M), derived from the nasal washings of a patient with a typical cold, which could be transmitted serially in human volunteers. This virus can be grown readily in tissue cultures of human or monkey kidney cells, provided they are maintained at a temperature around 33°C and in a medium of lower pH than is used in present-day routine virology. We have found that viruses with similar biological properties may readily be isolated from a substantial proportion of colds, though most of them have as yet been grown only in human embryo-kidney cells (Hobson and Schild 1960, Tyrrell and Bynoe 1961). Since the H.G.P. strain could be grown in monkey-kidney cells this was more convenient for a detailed study of the behaviour of these viruses in man.

Materials and Methods

The virus used as an inoculum consisted of three pools of washings collected from volunteers at the onset of colds

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experimentally induced by the inoculation of earlier washings.

The volunteers providing material for each pool were those showing colds in the 1st, 3rd, and 4th human passage of the virus; the 1st and the 3rd passages are shown in the figure of Hitchcock and Tyrrell (1960). These pools had infectivity titres of about $10^{3\cdot3}$, $10^{>1}$, and $10^{2\cdot3}$ TCD_{50} per ml. respectively, and when administered as nasal drops they produced colds in 3/6 (3 out of 6), 4/9, and 7/18 volunteers respectively.

The volunteers inoculated at Salisbury were between eighteen and forty-five years of age. They were isolated and observed as described by Andrewes (1948), and most were inoculated intranasally by dropping 0·5 ml. of 1/10 dilution of washings into each nostril. In certain experiments they were inoculated by dipping a damp swab into undiluted virus and stroking it on the fauces and posterior pharyngeal wall, on the conjunctiva, or on the anterior part of the nasal mucous membrane.

In the trials at Sheffield the volunteers were students between eighteen and twenty-six years old, who were not in isolation, and who were inoculated by nasal drops. Nasal washings were collected only from those volunteers who developed symptoms of a cold. Moreover, a group of 7 volunteers was inoculated with saline, and the clinical observer, who did not know the nature of the inoculum, did not think that any of these "control" volunteers developed colds. The results of the Sheffield trials are included with those of the Salisbury trials where appropriate; but there were these slight differences in procedure, and all the experiments on the effectiveness of different routes of inoculation and on repeated testing of volunteers for the presence of virus were done at Salisbury.

For virus isolation, throat or nose swabs were taken and stored at −60°C in bottles containing 3 ml. of Hanks' saline. Nasal washings were also collected in Hanks' saline or medium 199. The fluids from swabs and washings were inoculated in 0·3 ml. volumes into monkey-kidney cell cultures containing about 30,000 cells, and maintained as described by Tyrrell and Parsons (1960). The medium was changed after one day and again about five days later. The cultures were observed for ten to fourteen days, and, if there was a cytopathic effect, this was transmitted in almost all cases to further cultures. At least one strain from each volunteer was identified by a neutralisation test with specific immune serum prepared in rabbits.

Serum was collected from 49 volunteers shortly before inoculation, and again from 46 of them about two weeks after inoculation. The neutralising capacity of serum was estimated by measuring the reduction of the ability of a virus to produce microplaques (Parsons and Tyrrell 1961) after incubation at room temperature for two hours with a 1/20 or 1/200 dilution of inactivated serum. The method is based on the work of Burnet et al. (1937), Dulbecco et al. (1956), and others, and its evaluation will be described in full (D. Taylor-Robinson and D. A. J. Tyrrell, in preparation). The activity of the serum is represented by a constant indicating the rate at which serum inactivates virus in the early stages of the neutralisation process, which behaves approximately as a first-order reaction. The constant K is calculated from the formula:

$$\frac{\text{Number of plaques with serum}}{\text{Number of plaques without serum}} = e^{-K.120.C}$$

where C = concentration of serum in the reaction mixture, and 120 = the time in minutes during which serum and virus react together. A K value less than 0·1 signifies little or no virus inactivation by a 1/20 dilution of serum. A K value greater than 3·8 signifies almost complete inactivation by a dilution of 1/200. This type of neutralisation test is substantially more sensitive than the conventional end-point neutralisation test used in earlier experiments (Hobson and Schild 1960, Tyrrell and Parsons 1960), and since employing it we have had little difficulty in detecting antibody rises in the serum of volunteers, and in obtaining reproducible titres. Antibody rises of threefold or more were regarded as significant.

TABLE I—RESULTS OF INOCULATING VOLUNTEERS WITH HUMAN NASAL WASHINGS CONTAINING H.G.P. VIRUS

Place	Route of inoculation	No. of volunteers			
		Total inoculated	With colds	With colds and laboratory evidence of infection	Without colds but with laboratory evidence of infection
Sheffield	Nasal drops	16	6	6	Not tested
Salisbury	Nasal drops	16	6	5	2
,,	Nasal swabs	7	2	2	1
,,	Conjunctival swabs	7	2	1	0
,,	Throat swabs	8	0	0	0
Total		54	16	14	3

Results

We performed these experiments to try to answer a number of different questions in connection with the pathogenesis of this experimental disease, and the data will be analysed and presented as far as possible in relation to these questions.

Our first question was by what route could we most readily infect volunteers, and hence, what is the most likely route of infection under natural conditions?

It can be seen from table I that the experimental disease was most readily produced by virus given as nasal drops, although applications on nasal or conjunctival swabs were also at times successful. No colds were induced when the virus was given by means of throat swabs, even though some of the volunteers had very low levels of antibody in the serum (see below). The type of cold produced was that seen in previous experimental infections with this virus (see Tyrrell and Bynoe 1961).

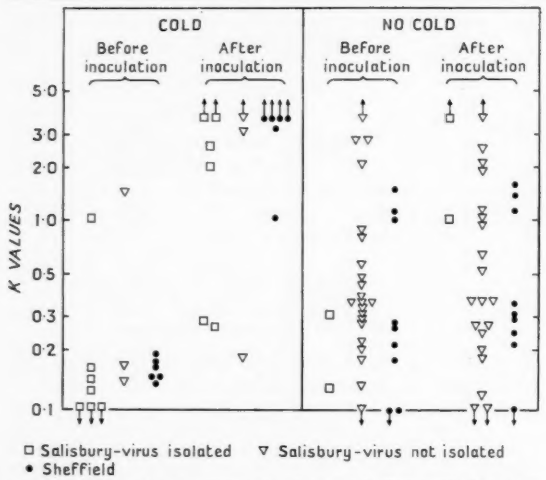
Our second question was when and where was virus excreted from the respiratory tract of volunteers?

TABLE II—RESULTS OF REPEATED SWABBING OF VOLUNTEERS WITH COLDS INDUCED BY H.G.P.

Volunteer	Virus recovered from swab taken after inoculation on days:				
	1	2	3	4	5
Be	0	+	+	0	0
Th	0	+	+	+	0
Su	0	0	+	0	0

There was laboratory evidence of infection (virus isolation, antibody rise, or both) in all but 2 volunteers who got colds, and there was evidence of infection in 2 volunteers without colds (table I). Virus was isolated from 9 of 38 volunteers at Salisbury, but in no case did conjunctival swabs give positive isolation. In 6 cases in which isolation was successful and repeated tests were made, a nasal swab alone was positive in 1 case, nasal or throat swabs and washings were positive in 2 cases, and nasal washings only in 3 cases. This was despite the fact that swabs were collected daily, but washings were collected only on the day on which cold-like symptoms appeared. Washing, therefore, seemed to be the best way of recovering virus. However, in experiments in which virus was successfully isolated from swabs we found that it might be detectable for only a short period during the experimental disease (table II). We have already shown that even using washings it may not be possible to isolate virus from more than two-thirds of a group of volunteers infected with cultivable viruses (Tyrrell and Bynoe 1961).

Combining the results obtained at Sheffield and Salisbury, we isolated virus from 13 out of 16 volunteers who developed colds, and from 12 out of 14 volunteers showing antibody rises.



Antibody levels in the serum of volunteers before and about two weeks after inoculation.

Volunteers who developed colds had low levels of antibody before inoculation and usually developed high levels afterwards. Volunteers who did not get colds had higher levels of antibody which generally remained unchanged. Virus was isolated from all Sheffield volunteers who had colds but isolations were not attempted from those without colds.

Virus was isolated from 2 volunteers in whose serum an antibody rise was not detected. Antibody rises were found in 12 of 15 cases in which virus isolation was successful, and in 1 of the 3 cases of colds in which virus was not recovered. The geometric mean neutralising antibody activity in the volunteers with colds was 0·18 before inoculation and 1·7 afterwards. Antibody rises ranged from threefold to more than thirtyfold, and the final antibody (K) levels in infected volunteers ranged from 0·21 to >3·8.

Our next question was whether the resistance which many volunteers showed to H.G.P. virus correlated with the level of circulating antibody at the time of inoculation?

The figure summarises the serological data, and shows that the volunteers who developed colds had, on the average, significantly lower antibody levels (G.M. 0·18) than those who did not develop colds (G.M. 0·46). Almost all (14 out of 16) volunteers who got colds had little or no antibody ($K < 0·22$), and the 2 with high levels had been inoculated by the conjunctival route. Only 7 of 33 volunteers who did not get colds had such low antibody levels. One would not expect that antibody in the blood-stream would be so effective in preventing infections of the surface of the nasal mucous membrane; but high titres of inhibitory activity have been found in nasal secretions collected from some normal subjects with antibody in the serum (M. Moffat, Y. Barr, and D. A. J. Tyrrell, unpublished), and the significance of this will be investigated further. We also intend to study the rate of decline of the serum-antibody levels in our volunteers.

Discussion

In our attempts to infect volunteers by various routes we tried to give the same amount of virus by swabs as by drops, but we may not have been entirely successful. The final number of colds produced was not large; nevertheless it seems that colds may be produced almost as readily by applying virus by nasal and conjunctival swabs as by giving nasal drops, and also that the throat may be relatively resistant to infection. We were surprised to find that colds were induced by virus administered on conjunctival swabs. There were no signs or symptoms localised to the eye, unlike the conjunctivitis produced when adenoviruses are swabbed on to the conjunctiva of volunteers (Huebner et al. 1955), nor was virus recovered from the conjunctiva. We think, therefore, that infection was initiated in the nose, and that the virus may have multiplied only after passing down the nasolacrimal duct into the nasopharynx; all the same it seems possible that, under natural conditions, the virus might sometimes reach the nasal epithelium via the conjunctiva rather than via the external nares. Papp (1959) has produced clinical evidence that measles virus may normally infect children via the conjunctiva, and Moore (1957) considers that salmonellæ usually spread among guineapigs by the conjunctival route.

14 out of 21 volunteers with antibody levels below $K = 0·22$ developed colds. We therefore think there is clear evidence that circulating antibody may protect against disease, and accordingly that vaccination might be an effective prophylactic. However, some volunteers with low antibody levels did not become infected, and there may be some non-specific resistance to infection. The results so far suggest that the specific immunity which Jackson and Dowling (1959) have shown after experimental colds is probably the result of specific antibody responses. They also contrast with some of our earlier experiments in which parainfluenza (Tyrrell et al. 1959) and J.H. viruses (Tyrrell and Bynoe 1958) were given to volunteers, with poor correlation between resistance to infection and the presence of circulating antibody. This may be because the viruses used were in fact adapted to tissue culture, or given in large doses.

Summary

54 human volunteers have been inoculated by various routes with pooled nasal washings containing the H.G.P. virus.

Colds were induced in 16 volunteers, who were mainly those receiving virus as nasal washings, but also in 2 of 7 volunteers who were given the virus by nasal swabbing, and in 2 of 7 who received it by conjunctival swabbing. Virus was isolated from volunteers most readily by means of nasal washings, and mainly from those with colds.

There was correlation between low levels of serum-antibody and the development of colds. Significant rises of antibody level were found during the illness of 11 of 15 volunteers with colds, but also in 3 out of 32 volunteers without colds.

We wish to thank the volunteers, without whose willing cooperation these experiments would have been impossible. We also thank Mr. J. W. May for laboratory assistance, and the Poliomyelitis Control Laboratories of the Medical Research Council at Hampstead for supplying monkey-kidney cells.

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ULTRASONICS IN THE DIAGNOSIS OF INTRACRANIAL SPACE-OCCUPYING LESIONS

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THE special properties of ultra high-frequency sound vibrations were first appreciated and applied by Langevin in 1918, through his work with the piezo-electric crystal. The technique of transmitting short pulses of low-intensity ultrasound into a medium under investigation, and then detecting and calculating the position of echoes reflected by any interface which lies in the path of the sound within this medium, is now widely used in industry —e.g., for detecting flaws in metal castings. The method is popularly known in the form of ASDIC for submarine detection and measurement of the depth of the sea bed. In Nature the principle is used by bats and porpoises for direction finding.

The Physics of Ultrasound

Sound vibrations of greater frequency than 20,000 c.p.s. are beyond the range of human hearing, and are therefore termed "ultrasonic". Compared with audible sound, ultrasound tends to travel in a straighter line, and has less tendency to scatter. Partly because of this and partly because of the mode of production, ultrasound can be made to beam in the manner of light; the higher the frequency the greater the tendency to beam.

The specific "acoustic impedence" (S.A.I.) of a material is defined as the product of the density of that material and the velocity of a sound wave within it. When an ultrasonic beam meets an interface between two substances of different S.A.I., some of the energy is reflected; the greater the difference in S.A.I., the greater is the proportion of energy reflected. The remainder of the sound is transmitted through the interface into the second medium, and is now attenuated. In addition some of the sound vibrations are absorbed and converted into heat, different media having different absorptive capacities.

Destructive Effects

Experimentally, ultrasonic vibrations will produce tissue damage or destruction only when employed at high intensities. All destructive effects seem to depend upon the phenomenon known as "cavitation". Briefly, the negative and positive pressures in a fluid, which accompany the successive rarefactions and compressions constituting the sound wave, cause dissolved gases to come out of solution in the negative phase and to collapse in the positive phase. The rapid formation and collapse of gas bubbles is believed to be responsible for cavitation.

Research into the application of ultrasonically induced lesions, both in therapy and in investigation, is being conducted on an elaborate scale, especially in the United States. Such destructive effects, however, do *not* arise with the much lower energies, high frequencies, and short pulses used in the diagnostic "echo-sounding" method, and they may be disregarded.

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Ultrasound in Medical Diagnosis

The first published work on the echo-sounding principle in medical diagnosis, by Wild (1950), was concerned with breast carcinoma. Since then, considerable progress has been made in several countries, notably by Wild and Neal (1951), Wild and Read (1954), and Howry et al. (1954) in the United States and Donald et al. (1958) in Britain.

The problems of echo-sounding in the head are made very much greater by the intact skull, which creates a significant barrier to the transmission of sound. Much energy is absorbed in the bone; indeed, such loss can account for a factor of 40–400 in intensity for the double path, varying with the thickness and density of the bone. Because of this, and because there are comparatively few workers in this special field, progress with ultrasonic diagnosis has been slower in the central nervous system than elsewhere. Leksell (1956, 1958) first described what has come to be known as echo-encephalography, and Kikuchi et al. (1957), Gordon (1959), and Vlieger and Ridder (1959) have written on this subject. Jefferson (1959) has described his experiences, and Lithander (1960) has reported 150 cases examined by this method.

During 1960, clinical trials were initiated in the department of neurosurgery of St. George's Hospital, at Atkinson Morley's Hospital, using an ultrasonic instrument specially designed and built in the department of physics at the Royal Marsden Hospital. To resolve small echoes from interfaces between tissues with a not very dissimilar acoustic impedence, a high sound-frequency is desirable. But the absorption of sound energy by tissue increases rapidly with rising frequency, and this absorption limits the effective frequency which can be used in practice. The Marsden instrument combines a working frequency as high as 2·5 Mc.p.s. with a sensitivity adequate to detect the resulting echoes, which are displayed as vertical pulses on a horizontal 15 cm. scale, marked on a cathode-ray tube. A common crystal, of commercial manufacture, is used both as transmitter and receiver. A detailed technical description of the instrument has been published elsewhere (Newell 1960).

Interpretation of Echoes

Various echoes are obtained from interfaces within the skull, the interpretation of which is uncertain. Our experience, which agrees with that of other workers, is that the most constant and usually the largest echo is derived from structures in the midline of the brain, and this is the object of study.

There is controversy as to the source of this midline echo, Leksell (1956) believing it to be the pineal body. We have no doubt that this is not invariably so, having detected displacement of the echo anteriorly by a frontal neoplasm in the presence of a well-calcified and undisplaced pineal, which was clearly demonstrated radiographically. As well as the pineal body, the superior longitudinal fissure, septum pellucidum, and third ventricle may, we believe, all contribute to this echo.

Pulsations

Vigorous pulsations and movement of echoes in all dimensions, synchronous with the heart beat, have been seen regularly and apparently independently of any pathological process within the brain. Such pulsation in a brain, shown later to be normal, may be greater than that in a brain with, say, a large vascular malformation. These pulsations, we believe are physiological, and they provide good evidence that the whole brain pulsates in an expansile manner within the intact skull.

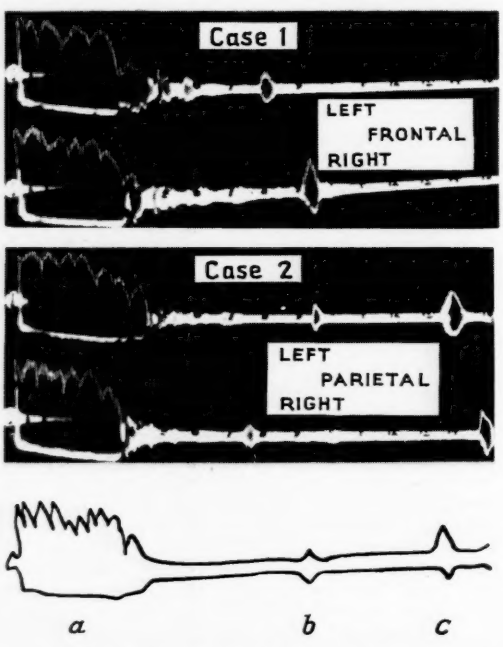
Clinical Method

The method of examination is extremely simple, and we regard the use of such a device as the "comparator", described by Gordon (1959) as an unnecessary complica-

tion. Surface contact between the crystal probe and the scalp must exclude air, and a satisfactory "coupling" medium has been found in glucose syrup *B.P.* We have never had the head shaved for an ultrasonic examination.

Being portable, the instrument may be carried to the bedside, and plugged into the mains electrical supply. The patient's head rests upon a sandbag, and the coupling fluid is liberally applied to the scalp with a gauze swab. The probe is applied to the head at a series of points, symmetrically, on either side. The hair can easily be flattened and incorporated into the fluid film at the point of application of the probe. The position of the midline echo is then measured on the graduated scale, and recorded for the frontal, temporal, and parietal portals. A significant displacement can be rapidly calculated from any difference in the measurements of the distance between the surface and the midline, as between symmetrically situated portals. Permanent photographic records are made with a camera attached to the instrument.

Adequate coupling and the proper display of echoes requires a little practice and involves some manipulation of the probe against the scalp. The use of two probes simultaneously on either side of the head (Gordon 1959), with the object of rendering a midline displacement immediately obvious, has little advantage and carries the very real disadvantage of requiring the examiner to manipulate two probes at once. An experimental error is inherent in the method, because both the shape of the skull and the manipulation necessary for coupling make exact symmetry of portals, and exactly tangential application of the probe to the midline, difficult or impossible to achieve. In practice an apparent displacement of 3 mm. or less has been regarded as within the limits of experimental error, and not significant.



Characteristic ultrasonic records showing significant midline displacement.

Case 1: midline measures 7·6 mm. from left frontal region, and about 9·2 mm. from right. Midline displacement = 8 mm. to left.

Case 2: midline measures 9·4 mm. from left parietal region, and about 7·6 mm. from right. Midline displacement = 9 mm. to right.

Explanatory line diagram: *a* = artefact caused by reverberation in crystal; *b* = midline echo; *c* = echo derived from opposite side of skull.

Diagnostic Results

Ultrasonic examinations have been performed on 280 patients (all admitted to hospital under the care of Mr. Wylie McKissock or Mr. Lawrence Walsh) with a variety of conditions, including cerebral neoplasm, cerebral abscess, intracranial hæmorrhage, head injury, and so on.

Of the 280 patients, 248 underwent further investigations such as carotid angiography or ventriculography. In 32, the ultrasonic findings were unverified; these all presented undisplaced midline echoes and an improving or recovering clinical course which did not justify further intervention.

The ultrasonic findings were:

Accurate prediction of space-occupying lesion	86 cases
Accurate prediction of absence of space-occupying lesion	130 ,,
Unverified prediction of absence of space-occupying lesion	32 ,,
Failure to predict a space-occupying lesion	17 ,,
False prediction of a space-occupying lesion	1 ,,
Unsatisfactory demonstration of echoes	12 ,,

Thus, of the verified cases, the accuracy rate was 216 out of 248, or 87%. The examination was misleading in 18 out of 268, or 7% of the total.

Failures

Of the 18 cases inaccurately predicted, 15 had space-occupying lesions either close to the midline or frontally, and measurement of the midline on radiographic studies —air or angiographic—showed the displacement to be small. These failures show that the method will not allow confident prediction of slight displacement. The other 3 cases, and the single false prediction of a non-existent shift, were entirely misleading and must be ascribed to observer error.

In 12 cases we could not display echoes of diagnostic quality, possible explanations being poor coupling and an unusually absorptive skull. But these 12 represent only 4% of the total.

Discussion

An accuracy record of about 90% is satisfactory for any special investigation in the central nervous system, and it is especially good for one which involves no discomfort or potential danger to the patient, and which takes only a few minutes. The only inconvenience is that of having applied to the hair sticky sugar solution, and this is freely soluble in water.

Although a method which merely detects the displacement of the midline structures above the tentorium has limitations, it has nevertheless proved genuinely helpful in the practice of St. George's neurosurgical department. Its diagnostic value in the acute head injury is obvious. It has been especially noteworthy in the differential diagnosis of acute cerebrovascular accidents, major arterial occlusions being regularly distinguished from space-occupying hæmatomas. Indeed, as an indicator of space-occupying hæmatomas, it has proved more sensitive than carotid angiography, being nearly as accurate as ventriculography. Of 35 cases of non-aneurysmal cerebrovascular accident, the diagnosis was predicted correctly on the ultrasonic findings in 32.

The detection and lateralisation by ultrasonics of a supratentorial space-occupying lesion when localising signs are few or absent has often indicated the most appropriate special investigation, and thus spared the patient, for example, from ventriculography or bilateral carotid arteriography. Conversely, a negative ultrasonic examination may reinforce a difficult clinical decision to

withhold or defer special investigations. We have no outpatient experience of the ultrasonic instrument, but we think it might be of some value in assisting the sometimes difficult decision to admit to hospital a patient, suspected of harbouring a space-occupying lesion, for special neuroradiological procedures.

Clearly, it is desirable to identify, and interpret with confidence, several echoes other than those from the midline, which are often seen, and which are probably derived from ventricle walls, major fissures, and possibly deep nuclei. But we think this will be possible only with a more elaborate scanning technique, comparable to that already successfully employed for the pelvis and abdomen by Donald in Glasgow (Donald et al. 1958). Work is at present in progress on such a scanning device for the skull, and clinical trials are planned for the near future. In our view, however, even in its present simple form, the ultrasonic instrument has earned a place in the routine diagnostic armamentarium of a neurosurgical department.

We wish to thank Prof. W. V. Mayneord, of the department of physics, the Royal Marsden Hospital, and Mr. Wylie McKissock, of the department of neurosurgery, St. George's Hospital, for much encouragement and advice.

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OBSERVATIONS ON A CASE OF PYRIDOXINE-RESPONSIVE ANÆMIA

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THERE is evidence that pyridoxal phosphate is necessary for hæm synthesis (Schulman and Richert 1957). Hypochromic anæmia develops in animals fed on pyridoxine-deficient diets (Wintrobe et al. 1943, Poppen et al. 1952), and Snyderman et al. (1953) observed anæmia in an infant given such a diet.

In 1956 Harris et al. described the first case of a naturally occurring anæmia in man which responded to pyridoxine. Six other cases of pyridoxine-responsive anæmia have since been published.

We report observations on a patient with an iron-refractory hypochromic anæmia that responded to pyridoxine. Data obtained with ^{59}Fe suggested that considerable ineffective erythropoiesis was taking place before treatment. Red-cell life, which was short before treatment, became normal after pyridoxine therapy.

Case-report

This man was first seen in the skin department of St. Thomas's Hospital in 1953, when he was 23, with a rash which had been present for three years. The classical skin changes of pityriasis rubra pilaris were present (Dr. H. J. Wallace). No family history of skin disease was obtained. He has attended the skin department regularly since 1953, but no treatment has affected the condition of his skin.

In July, 1955, he was found to be anæmic (hæmoglobin 9·4 g. per 100 ml.) and was given ferrous sulphate and liver extract.

In December, 1956, he was admitted to St. Thomas's Hospital. He had not had dyspepsia or gastrointestinal bleeding. The spleen tip was palpable, but the liver could not be felt. A blood-count showed: Hb 11·2 g. per 100 ml.; red cells $5{\cdot}7 \times 10^6$ per c.mm.; hæmatocrit value 39%; mean corpuscular hæmoglobin concentration (M.C.H.C.) 28%; mean cell-volume (M.C.V.) 68 c.μ. A blood-film showed hypochromia and anisocytosis; reticulocytes 0·5%; white blood-cells (W.B.C.) 6600 per c.mm. (neutrophils 68%, lymphocytes 21%, monocytes 4%, eosinophils 6%, basophils 1%); erythrocyte-sedimentation-rate (E.S.R.) 7 mm. in the first hour (Westergren). The patient declined a sternal marrow puncture. Tests for occult blood in the stools were positive twice and negative once. Other investigations showed: serum-bilirubin 0·8 mg. per 100 ml.; thymol turbidity 1 unit; alkaline phosphatase 4·5 King-Armstrong units; total plasma proteins 7·1 g. per 100 ml.; plasma-albumin 4·6 g. per 100 ml.; plasma-globulin 2·5 g. per 100 ml.; plasma-carotene, nil; plasma-vitamin-A level, about 12 I.U. per 100 ml. The plasma-vitamin-A level rose to 1113 I.U. per 100 ml. after treatment with vitamin A by mouth. The stools contained 18% of fat by weight of the dried stool.

During the next two years he received ' Ferrivenin ' (20 ml.), ' Imferon ' (25 ml.), and almost continuous ferrous sulphate therapy by mouth. The hæmoglobin level varied from 8·7 to 11·7 g. per 100 ml. and the M.C.H.C. was 27–28% (fig. 1).

Investigation of Anæmia

In March, 1959, the patient was referred for investigation as a case of iron-refractory hypochromic anæmia. He was rather breathless on exertion. He seemed well nourished, and weighed 70 kg. The tongue and nails appeared normal. The spleen was palpable 4 cm. below the left costal margin, and the liver 3 cm. below the right costal margin. The urine contained no sugar, albumin, bile, or excess urobilinogen.

No family history of anæmia was obtained. The patient, who has no children, was of English and Welsh ancestry. His mother and father have normal hæmoglobin levels (14·2 and 14·7 g. per 100 ml. respectively), and examination of their blood-films showed no abnormality. He has two brothers, but we could not examine their blood.

The blood-count was: Hb 11·5 g. per 100 ml.; hæmatocrit value 39%; M.C.H.C. 30%; red-cell count $5{\cdot}6 \times 10^6$ per c.mm; M.C.V. 70 c.μ. A blood-film showed red-cell anisocytosis. Some red cells seemed normal in size and hæmoglobin content, but the remainder were microcytic and showed varying degrees of poikilocytosis or ovalocytosis. Hypochromia was prominent in the abnormal cells There were occasional target cells and cells of bizarre shape.

The reticulocyte-count varied between 0·5% and 2·5%. The direct antiglobulin test was negative. W.B.C. 4400 per c.mm. (neutrophils 74%, lymphocytes 20%, monocytes 4%, eosinophils 1%, basophils 1%); platelets 300,000 per c.mm.; E.S.R.: 3 mm. in the first hour (Westergren). No occult blood was found in seven consecutive stool samples. The plasma-iron was elevated to 345 μg. per 100 ml. The red-cell osmotic fragility was normal. The alkali-resistant fraction of the hæmoglobin was less than 2%. Paper electrophoresis showed no abnormal hæmoglobin fraction and no increase in the A^2 fraction (Dr. J. A. M. Ager). The serum-vitamin-B_{12} level was normal (375 $\mu\mu$g. per ml.).

Sternal marrow aspiration was refused at this time, but was performed two months later. It showed normoblastic hyper-

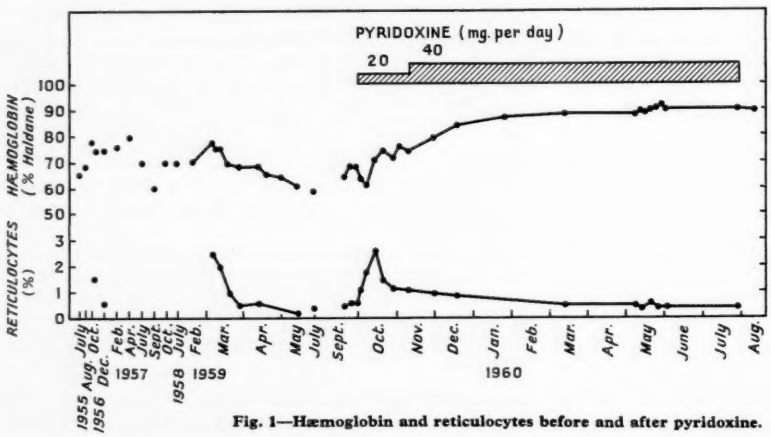
PYRIDOXINE (mg. per day)
20
40
HÆMOGLOBIN (% Haldane)
RETICULOCYTES (%)
1955 1956 1957 1958 1959 1960
July Aug. Oct. Dec. Feb. Apr. July Sept. Oct. July Feb. Mar. Apr. May July Sept. Oct. Nov. Dec. Jan. Feb. Mar. Apr. May June July Aug.

Fig. 1—Hæmoglobin and reticulocytes before and after pyridoxine.

plasia. Some of the late normoblasts were of the type usually associated with iron-deficiency anæmia. Staining for free iron showed iron in the cytoplasm of a large proportion of the intermediate and late normoblasts. Marrow-particle section showed free iron in reticuloendothelial cells. The following differential count was made:

Segmented polymorphs ..	10%	Basophilic normoblasts ..	11%
Band polymorphs ..	6·5%	Polychromatic normoblasts	26%
Metamyelocytes	2%	Orthochromatic normoblasts	20%
Myelocytes	11%	Lymphocytes	8%
Leucoblasts	1·5%	Plasma-cells	1·5%
Eosinophils	0·5%	Leucoerythrogenetic ratio ..	1/3
Proerythroblasts	3%		

During the next five months the hæmoglobin level fell steadily to 8·7 g. per 100 ml.; the reticulocyte-count fell in one month to 0·5%, and then varied from 0·3% to 0·6% (fig. 1). The M.C.H.C. during this time was 28%.

Treatment with Pyridoxine

In October, 1959, treatment with pyridoxine by mouth was started. 20 mg. daily was given for six weeks, and the dose then increased to 40 mg. daily. Fig. 1 shows the response. The reticulocyte-count rose from 0·5% to 2·5% in ten days. The hæmoglobin rose slowly to 13 g. per 100 ml. in three months, and remained between 13·0 and 13·7 g. per 100 ml. During the previous five years the hæmoglobin level was never found to be more than 11·7 g. per 100 ml.

In May, 1960, the following hæmatological data were obtained: Hb 13·3 g. per 100 ml.; hæmatocrit value 44%; red-cell count 5×10^6 per c.mm.; M.C.H.C. 30%; M.C.V. 88 c.μ. Examination of a blood-film now showed a greater proportion of normal cells, though a minority of microcytic irregularly shaped cells were still present. Reticulocytes 0·4%; direct antiglobulin test, negative; W.B.C. 6100 per c.mm. (neutrophils 70%, lymphocytes 29%, eosinophils 1%); platelets 159,000 per c.mm.; plasma-iron 318 μg. per 100 ml.

The patient's effort tolerance had improved subjectively. The size of the spleen and liver remained unchanged.

After ten months the pyridoxine therapy was stopped. Four weeks later a tryptophan-loading test was performed. "Chromatography of urine after a tryptophan load (70 mg. per kg. of *dl*-tryptophan) showed a normal excretion of tryptophan metabolites with the exception that no anthrallic acid was present. This is not typical of pyridoxine deficiency" (Dr. D. C. Cushworth).

Three months after pyridoxine therapy had been stopped the patient's hæmoglobin level had fallen to 10·2 g. per 100 ml., and the M.C.H.C. to 25·5%.

The Mechanism of Anæmia

Methods of Investigation

^{51}Cr.—The technique used to label red cells with ^{51}Cr was that of Jones et al. (1960), with the exception that in the studies on this patient the red cells were washed twice in isotonic saline after exposure to $Na_2{}^{51}CrO_4$ (specific activity about 20 mC. per mg.). The ^{51}Cr-red-cell survival was followed from samples taken as shown in figs. 2–4. The hæmatocrit value was measured in nine of the eleven samples in the first ^{51}Cr study, and in all samples in the second ^{51}Cr study. During the first study the hæmatocrit values varied between 38% and 39%, and between 41·5% and 42·5% in the second. No correction for changes in hæmatocrit value was made.

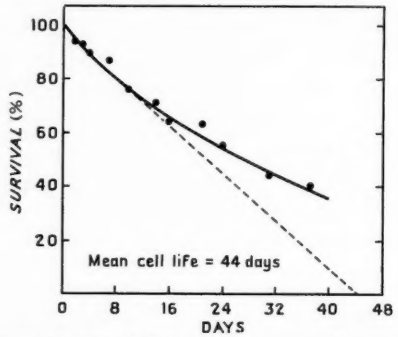

Fig. 3—Survival of Cr-labelled red cells, corrected for Cr elution by method "B".

^{59}Fe.—Plasma ^{59}Fe clearance and the utilisation of ^{59}Fe for hæmoglobin synthesis were determined after the injection of 10 μC ^{59}Fe as ferric citrate in normal saline (Wetherley-Mein et al. 1956). Plasma-iron turnover was calculated from the formula of Bothwell et al. (1957).

Plasma-iron levels were measured by the method of Bothwell and Mallett (1955).

Results

^{51}Cr studies before treatment with pyridoxine.—The red-cell volume was 24·4 ml. per kg. ^{51}Cr-labelled red cells disappeared from the patient's circulating blood more quickly than normal, 50% of the ^{51}Cr having been removed by nineteen and a half days (normal half-time roughly twenty-six days).

^{51}Cr studies seven months after pyridoxine therapy.—The red-cell volume was 27·6 ml. per kg. The rate of disappearance of ^{51}Cr from the patient's circulation was now normal (half-time = twenty-five and a half days).

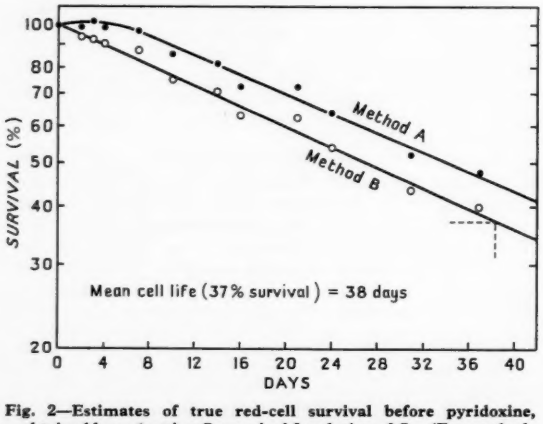

Fig. 2—Estimates of true red-cell survival before pyridoxine, obtained by correcting Cr survival for elution of Cr. (For methods "A" and "B" see text.)

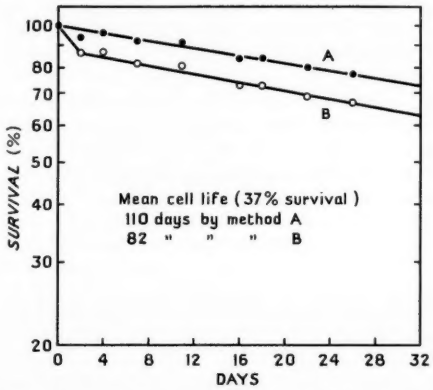

Fig. 4—Estimates of true red-cell survival after pyridoxine, obtained by correcting Cr survival for elution of Cr.

The problem of converting the ^{51}Cr-survival curve to a curve representing true red-cell survival has been thoroughly considered by Mollison and Veall (1955) and Mollison (1959), among others. Two main methods of allowing for ^{51}Cr elution from intact cells are in use:

Method " A " (Hughes Jones and Mollison 1956) employs empirical corrections which convert the normal ^{51}Cr-survival curve into the normal red-cell survival curve. Correction is thus made for the elution of ^{51}Cr that occurs from normal ^{51}Cr-labelled cells, and for the " early loss " of 8–10% of the injected ^{51}Cr with a half-time of about one and a half days that takes place in normal subjects.

Method " B " employs corrections which assume a steady rate of ^{51}Cr elution (Ebaugh et al. 1953); and this method ignores the " early loss " of ^{51}Cr.

Fig. 2 shows the ^{51}Cr red-cell survival curve obtained in our untreated patient after correction by both methods.

The corrected values for red-cell survival are plotted logarithmically against time, and the time of 37% survival is taken to indicate the mean cell lifespan (Dornhorst 1951). Method " B " yields a straight line, reaching 37% survival at thirty-eight days. Method " A ", however, yields a curve which is initially convex upwards. This observation may mean that the normal " early loss " of ^{51}Cr did not take place in our patient so that method " A " initially overcorrects the survival curve. Mollison (1959 and personal communication) has obtained the same results in a patient with a mild hæmolytic anæmia.

The uncorrected figures for ^{51}Cr survival in our patient were well within the normal range for the first seven days of the study, but then fell below the normal values. This may be due to absent or diminished elution of ^{51}Cr in the first few days concealing the decreased survival of the patient's red cells. Sufficient obscurity still surrounds the problem of early ^{51}Cr elution to make this interpretation tentative only.

This patient may have an intrinsic red-cell defect, and there are theoretical grounds for obtaining mean red-cell lifespan in such a patient from the initial slope of the red-cell survival curve plotted arithmetically. Such a slope is extrapolated to the time axis to provide an estimate of mean red-cell survival (Dornhorst 1951, Mollison 1960). Fig. 3 shows the patient's red-cell survival curve, corrected by method " B ", and handled in this way. The estimate of mean cell life is forty-four days which agrees well with the figure of thirty-eight days obtained.

After pyridoxine therapy correction of the survival curve by method " A " no longer showed initial overcorrection and the mean red-cell lifespan was now about one hundred and ten days (fig. 4).

We conclude that before treatment the red-cell lifespan was about forty days, and the normal " early loss " of ^{51}Cr may possibly have been diminished or absent. After treatment the red-cell lifespan was normal, or near normal, and " early loss " of ^{51}Cr took place normally.

^{59}*Fe studies before and after treatment with pyridoxine* (see table).—The plasma half-clearance time of ^{59}Fe was shorter than normal and the plasma-iron turnover was increased to about eight times normal. The build up of ^{59}Fe in the circulating red-cell mass was slower than normal and reached a final figure of only 47% of the administered dose.

Seven months after treatment the plasma-iron level had not fallen, and the utilisation of ^{59}Fe for hæmoglobin production had not altered significantly.

Hæmoglobin production before and after pyridoxine.—During the pretreatment ^{51}Cr study the hæmoglobin was relatively constant at 11·5 g. per 100 ml. We therefore assumed a steady state of red-cell production and destruction at this time. The total blood-volume, as calculated from the ^{51}Cr red-cell volume and the hæmatocrit value, was 73·6 ml. per kg. The red-cell life was about forty days. Thus, the hæmoglobin production was 0·2 g. per kg. per day (about twice normal).

During the ^{51}Cr study after treatment hæmoglobin production was about 0·1 g. per kg. per day.

Red-cell chemistry.—The following results were obtained by Dr. T. A. J. Prankerd: glutathione level normal; glutathione stability normal; ^{32}P uptake normal; metabolic-stress test normal; red-cell lipids normal.

^{59}FE STUDIES BEFORE AND AFTER PYRIDOXINE TREATMENT

—	Plasma iron µg. per 100 ml.)	Half-time ^{59}Fe clearance (min.)	Plasma-iron turnover (mg. per 100 ml. blood per day)	^{59}Fe utilisation (%)
Before treatment	345	42	5·0	35 (7th day) 47 (max.)
After treatment..	318	>	>	42 (7th day)
Normal values ..	70–180	70–140	0·38–0·77* (mean 0·61)	70–100 (7th day)

* Bothwell et al. (1957).

Discussion

Before treatment with pyridoxine the mean red-cell life was about forty days, and though hæmoglobin production was about twice normal this was insufficient to maintain normal hæmoglobin levels. The discrepancy between effective erythropoiesis, as indicated by hæmoglobin production (about twice normal), and plasma-iron turnover (about eight times normal) reflects the fact that the latter is a measure not only of effective erythropoiesis, but also of ineffective erythropoiesis, and of ^{59}Fe turnover through non-erythropoietic pools (Wetherley-Mein and Hutt 1960). Ineffective erythropoiesis has been described in pernicious anæmia (London and West 1950, Hallberg 1955, Bothwell et al. 1957), thalassæmia (Sturgeon and Finch 1957), and in other isolated cases of anæmia (Garby et al. 1957), and would explain the data obtained in our patient.

After pyridoxine therapy the mean red-cell life became normal and though hæmoglobin production was lower than before treatment, it was now sufficient to maintain a higher hæmoglobin level.

This patient's anæmia resembles that of thalassæmia major in showing red-cell hypochromia, despite an elevated plasma-iron level and abundant free iron in marrow sections, shortened red-cell life, and ineffective erythropoiesis. It differed from thalassæmia in the following features: (1) the blood-films and hæmoglobin levels of both parents of the patient were normal and there was no other evidence of a familial anæmia; (2)

there was no elevation of fœtal hæmoglobin, or of the A_2 hæmoglobin component; and (3) many of the patient's red cells appeared to contain normal amounts of hæmoglobin.

The cases of refractory normoblastic anæmia described by Dacie et al. (1959) resemble this anæmia in the appearance of the marrow normoblasts, the suggestion of two red-cell types in blood-films, the lack of response to iron, the evidence of ineffective erythropoiesis, and the shortened red-cell life span in some cases. In the cases reported by Dacie et al., however, the M.C.H.C. was normal and the M.C.V. was high, despite the presence in films of some hypochromic microcytes. Furthermore, six of Dacie's seven cases had received pyridoxine therapy without success.

The patient also had a rare skin disease, pityriasis rubra pilaris, but this is not usually accompanied by anæmia.

Naturally occurring anæmias which responded to pyridoxine have been described by Harris et al. (1956), Maier (1957), Gehrmann (1958), Leeming and Wilkinson (1959), Bishop and Bethel (1959), Verloop and Rademaker (1960), and Erslev et al. (1960).

The anæmia in these cases was microcytic with prominent anisocytosis and hypochromia. Some authors comment on bizarre red-cell forms and describe occasional target cells. The marrow was normoblastic, except in the patient of Maier (1957) in whom erythropoiesis was megaloblastic. Sideroblasts were usually prominent in marrow sections stained for iron. Plasma-iron levels were raised or high normal when measured. ^{51}Cr red-cell survival was measured by Harris et al. (1956) and by Verloop et al. (1960): in each case the survival was reduced, with half-times of twenty and eighteen days respectively. In these patients with pyridoxine-responsive anæmia the spleen was palpable in some but not in others. White-cell and platelet counts were usually normal.

Thus, patients with pyridoxine-responsive anæmia described to date have many similarities, chief among which is the presence of hypochromic, microcytic anæmia despite a raised or normal plasma-iron level, and abundant iron in the marrow. This combination suggests a defect in the utilisation of iron for hæm synthesis.

Pyridoxal phosphate is necessary for the activation of glycine before its union with succinate in the formation of δ-aminolævulinic acid (Schulman and Richert 1957, Kikuchi et al. 1958), probably via the intermediary formation of α-amino-β-ketoadipic acid (Shemin et al. 1955). The production of δ-aminolævulinic acid is an early stage in the biosynthesis of hæm, and deficiency of pyridoxine might therefore interfere with hæm formation.

The problem is the pathogenesis of the pyridoxine "deficiency" in the reported human cases. With the possible exception of the case reported by Verloop et al. (1960) dietary deficiency does not seem to be the cause. No evidence of malabsorption has been found when this has been sought, though our patient had unexplained low serum-carotene levels, as did that of Erslev et al. (1960). The excretion of abnormal urinary metabolites, particularly xanthurenic acid, after a tryptophan load is a sensitive indicator of pyridoxine deficiency (Greenberg et al. 1949). This test gave abnormal results in some reported cases of anæmia responsive to pyridoxine (Harris et al. 1956, Erslev et al. 1960); but it provided no evidence of pyridoxine deficiency in the present case or in those of Bishop et al. (1959) and Verloop et al. (1960). In our patient, however, the test was performed after pyridoxine therapy had been discontinued for only four weeks. Nevertheless, it seems more accurate to describe these cases of anæmia as pyridoxine-responsive rather than pyridoxine-deficient.

Bishop and Bethell (1959) suggested that in their patient excessive iron stores led to the formation of inactive iron-pyridoxal complexes thus interfering with pyridoxal function. This block was thought to have been overcome by the massive pyridoxine therapy. Most patients, however, with hæmochromatosis do not become anæmic; there was no evidence of excessive iron stores during remissions in the patients reported by Harris et al. (1956) and Erslev et al. (1960); and, finally, our patient responded to much smaller doses of pyridoxine by mouth than were used by Bishop and Bethell (1959), though the dose was still much larger than normal daily requirements.

Dacie et al. (1959) and Erslev et al. (1960) discuss the possibility that an excessive demand for pyridoxine is responsible for the "deficiency" resembling the relative deficiency of folic acid that may arise in chronic hæmolytic anæmias (Jandl and Greenberg 1959, Chanarin et al. 1959). If this is correct, it is difficult to understand why pyridoxine-responsiveness is so uncommon. Furthermore, if pyridoxine acted in our patient by correcting such a "relative deficiency", one would have expected it to have increased hæmopoiesis without correcting the abnormality in red-cell survival.

After pyridoxine therapy the hæmoglobin level in our patient approached the normal range without quite becoming normal. Such an incomplete response has been a feature of most reported cases of pyridoxine-responsive anæmia. In pigs (Wintrobe et al. 1943) and dogs (McKibbin et al. 1942) rendered pyridoxine-deficient the anæmia may be only partially corrected by pyridoxine, suggesting that the deficiency has produced a permanent defect in hæmopoiesis.

Reported cases of pyridoxine-responsive anæmia, despite many similarities, show sufficient variation to render grouping them as a homogeneous syndrome inadvisable at present.

Summary

A patient had an iron-refractory hypochromic anæmia which responded to pyridoxine.

Before treatment red-cell life was short, and there was evidence of ineffective erythropoiesis. After pyridoxine therapy red-cell life became normal.

Evidence was obtained that early elution of ^{51}Cr from red cells was reduced, but became normal after treatment.

Other cases of pyridoxine-responsive anæmia are reviewed and the role of pyridoxine in hæmopoiesis is discussed.

Our thanks are due to Dr. H. J. Wallace for permission to report this case; to Dr. T. A. J. Prankerd for the investigations of erythrocyte chemistry; to Dr. D. C. Cushworth who performed the tryptophan-loading test; to Dr. P. L. Mollison, Dr. Gordon Wetherley-Mein, and Dr. I. H. Mills for helpful criticism and advice.

Addendum

Treatment with pyridoxine had a less impressive effect the second time. The hæmoglobin level rose from 10·2 g. to 11·7 g. per 100 ml., and the M.C.H.C. from 25·5% to 28%. This hæmoglobin level has been maintained for a further seven months.

In several of the other reported cases the response to pyridoxine was incomplete and has varied from time to time. This increases the difficulty of defining the role of pyridoxine in hæmopoiesis.

References at foot of next column

VARIATIONS IN THE MORPHOLOGICAL PATTERNS OF "AUTOIMMUNE" NUCLEAR FLUORESCENCE

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DURING an investigation of the antinuclear factors in the serum of patients with Sjögren's syndrome (granulomatous atrophy of lacrimal and salivary glands, often associated with rheumatoid arthritis), disseminated lupus erythematosus, and other so-called collagen diseases by the fluorescent-antibody technique, variations were noted in the patterns of nuclear staining in tissue sections. I have now been able to separate and identify three different antinuclear factors by this method. Of these, one pattern is familiar but the other two are not.

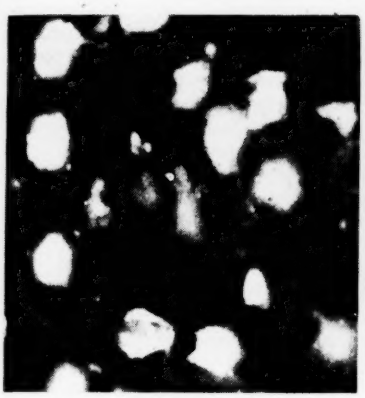

Fig. 1—Homogeneous staining. (× 775.)

Fig. 2—Speckled staining. (× 775.)

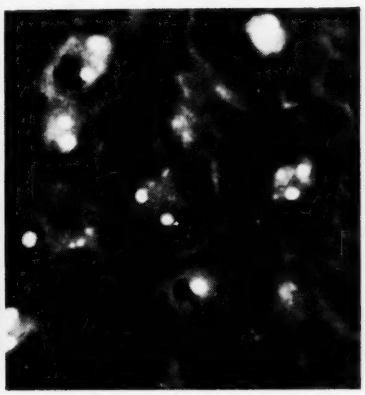

Fig. 3—Nucleolar staining. (× 775.)

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Materials and Methods

Unfixed cryostat sections of snap-frozen rat liver were used as a source of nuclei in most experiments. The sections were treated with the patient's serum for 30 minutes to allow attachment of antinuclear factor to the nuclei, washed for 10 minutes in barbitone-buffered saline (pH 7·2) with gentle agitation, and treated for 30 minutes with fluorescein-conjugated rabbit anti-human γ-globulin (prepared by the method of Riggs et al. 1958). This allowed the specific attachment of the fluorescent antibody to the patient's fixed γ-globulin, and excess was removed by washing for 10 minutes. The section was mounted in buffered glycerol (pH 7·2), and examined by dark-field blue-violet/ultraviolet light. All positive serum specimens were tested at quadrupling dilutions, using both rat-liver and frog-liver sections. The highest dilution causing detectable nuclear fluorescence by this method was regarded as the end-point of the titration. Controls using normal human serum and also fluorescein-labelled anti-human serum-albumin were negative.

Results

Three distinct patterns of nuclear fluorescence were seen in sections of rat liver "stained" with the serum from thirty patients:

Homogeneous.—The nucleus was stained throughout but often showed some moderately large irregular areas of somewhat more intense fluorescence (fig. 1).

Speckled.—The nucleus showed numerous minute uniform points of fluorescence scattered throughout its substance. Because the speckles were sparse at the periphery of the nucleus its margins were indistinct (fig. 2). These speckles were readily distinguishable from the areas of brighter fluorescence seen in the homogenous pattern of staining, which are pleomorphic and appreciably larger.

Nucleolar.—Here intense homogenous staining of the nucleolus was associated with dull homogenous fluorescence of the rest of the nucleus (fig. 3).

Most sera showed the same pattern of staining at all concentrations. Some strong sera produced an overall staining of the nucleus with superimposed speckling, but on further dilution the homogeneous staining was lost, and the nuclei showed the typical speckled pattern. These specimens were classified as the "speckled" type. The frequency of the different staining patterns in the serum of the patients studied is shown in table I.

A selection of serum specimens representing the three types was used to stain fresh frozen liver sections from the rabbit, ferret, cotton-rat, mouse, hamster, guineapig, hen, and frog. In all except frog liver, the patterns of nuclear staining were similar to those in rat liver. When all the sera were titrated

TABLE I—ANTINUCLEAR FACTOR PATTERNS IN SERUM OF 30 PATIENTS

Disease	No. of cases	Homogeneous staining	Speckled staining	Nucleolar staining
Sjögren's syndrome	12	5	7	1
Systemic lupus erythematosus	7	3	4	..
Cutaneous " "	3	2	1	..
Acrosclerosis	2	..	2	..
Rheumatoid arthritis	5	4	1	..
Dermatomyositis	1	..	1	..
Total	30	14	16	1

with frog liver sections the titres of the "homogeneous" specimens were closely parallel with those of rat liver, whereas some "speckled" specimens were negative. When the serum gave both homogeneous and speckled staining of rat liver, it produced homogeneous staining of frog liver of much lower titre. The nucleolar-staining titre was identical for frog and rat liver.

When rat testis was examined, all types of serum produced nuclear staining of their characteristic pattern in spermatogonia and Sertoli cells, but they did not stain the nuclei of mature spermatozoa.

When the "nucleolar" serum was used to stain a variety of rat tissues, the cytoplasmic staining was always of low intensity even in areas of high ribonucleic-acid concentration, such as Nissl's substance of nerve-cells.

Both speckled and homogeneous antinuclear factors reacted well within the pH range 5–8, but staining was most intense between pH 6 and 7. Most serum reacted equally well at 4°, 17°, and 37°C, although several homogeneous and speckled serum specimens of high titre were inactive or produced less intense staining at 37°C.

All patterns of nuclear staining were barely affected by fixation of the section in absolute acetone for 10 minutes at room temperature. Staining was much less intense after 10 minutes in absolute ethanol at room temperature, while the patterns produced by the speckled and homogeneous serum became indistinguishable because of clumping of the nucleus by this fixation. Fixation in 70% ethanol for 5 minutes at room temperature virtually prevented subsequent staining.

The speckled antigen was rapidly removed by washing the section with 0·15 *M* saline (pH 4–8) or with *M* saline (pH 7), whereas the homogeneous antigen was slowly extracted to form radiating strands when treated with *M* saline (pH 7) but was unaffected by 0·15 *M* saline (pH 4–8).

Unfixed and acetone-fixed rat-liver sections were treated with Worthington deoxyribonuclease and Worthington ribonuclease, with appropriate controls, before treatment with the three staining systems. The results are shown in table II.

Deoxyribonucleoprotein, isolated from calf thymus by the low ionic strength method (Chargaff 1955), was stained by the homogeneous but not by the other antinuclear serum specimens. Histone and "nuclear globulin", prepared by the method of Monty and Dounce (1959) from calf-liver nuclei (isolated in 0·25 *M* sucrose, pH 6), were not stained by any serum.

The antinuclear factor responsible for homogeneous nuclear staining was effectively absorbed from serum by treatment with calf thymus deoxyribonucleoprotein, but it was not absorbed by deoxyribonucleic acid (D.N.A.) or histone separately. Treatment of speckled and nucleolar antinuclear serum with deoxyribonucleoprotein, D.N.A., histone, nuclear globulin, mouse-liver ribonucleic acid, or yeast ribonucleic acid did not reduce their staining titres.

TABLE II—EFFECT OF ENZYMES ON NUCLEAR ANTIGENS

Enzyme	Speckled antigen	Homogeneous antigen	Nucleus	Nucleolus
Deoxyribonuclease	−	−	−	−*
Buffer control	−	+ +	+	+ +
Ribonuclease	+ +	+ +	+	−
Distilled water	+ +	+ +	+	+ +

* Deoxyribonuclease did not prevent staining if section was fixed in absolute acetone for 10 minutes before exposure to the enzyme.

Discussion

The different patterns of nuclear fluorescence produced by the three types of serum probably indicate the presence of three different antinuclear factors specific for three separate nuclear antigens. Most of the serum specimens showed a progressive diminution in staining intensity, without alteration in pattern, during titration; so it seems likely that only one antinuclear factor is detected by the Coons technique in each case, and that the staining pattern is not determined by the concentration of the antinuclear factor. Furthermore the homogeneous antigen is present in frog as well as mammalian tissue, whereas the speckled antigen is restricted to the mammalia. The few serum specimens which show the mixed speckled and homogeneous patterns when tested at high concentrations probably possess both the speckled and homogeneous antinuclear factors, with the latter at lower concentration.

Investigations were undertaken to try to identify the antigens responsible for the three different patterns of nuclear fluorescence. The evidence for each is summarised below.

Homogeneous staining.—The antigen is present in the nuclei of all somatic cells of the rat in which D.N.A. is combined with histone as nucleohistone, but it is absent from the nuclei of spermatozoa where the D.N.A. is present as nucleoprotamine. The antigen is removed by incubation of the section with deoxyribonuclease before staining, and it is partially extracted by *M* saline in the same way as deoxyribonucleoprotein. It is present in isolated deoxyribonucleoprotein, and the antinuclear factor is absorbed from the serum by deoxyribonucleoprotein but not by D.N.A. or histone separately. This suggests strongly that the homogeneous staining is caused by an antibody to deoxyribonucleoprotein similar to that described by Holborow and Weir (1959) and Holborow (1960). The antigen does not seem to be species specific, and in this respect it is similar to the antibodies to deoxyribonucleoprotein detected by other immunological techniques (Cappellini et al. 1957, Meischer and Strässle 1957, Christian et al. 1958, Seligman 1958).

Speckled staining.—The antigen responsible for this staining pattern is present in somatic cells of mammals, but it is absent from their spermatozoal nuclei and from frog somatic cells. Unlike deoxyribonucleoprotein it is rapidly removed by washing with 0·15 *M* isotonic saline but not with distilled water. The antigen is unaffected by treatment with ribonuclease, but I have not been able to determine the effect of deoxyribonuclease on the antigen because it is extracted by the control buffer solution. Staining and absorption experiments were negative with D.N.A., deoxyribonucleoprotein, histone, nuclear globulin, mouse-cytoplasm ribonucleic acid, and yeast ribonucleic acid. So far this antigen has not been identified; but, in view of its great solubility in 0·15 *M* saline, it may be one of the soluble proteins which Barton (1960) has identified in liver nuclei.

Nucleolar staining.—This pattern of staining has not been recorded previously, and there was only one example in my series. The antigen was found in the nucleoli of all mammalian and frog somatic cells examined except spermatozoal nuclei. The antigen was not readily extracted by distilled water, or by 0·15 *M* or *M* saline. Staining was prevented by pretreatment of the section with ribonuclease, but the antinuclear factor was not absorbed from the patient's serum by absorption with

mouse-liver cytoplasmic ribonucleic acid, yeast ribonucleic acid, or the other isolated nuclear constituents. This apparent inconstancy probably implies that the nucleolar ribonucleic acid is antigenically distinct from cytoplasmic ribonucleic acid. It is compatible with the evidence (reviewed by Sirlin 1960) that the structural ribonucleic acid of the nucleolus shows chemical and metabolic differences from the soluble nucleolar ribonucleic acid which is apparently related to cytoplasmic ribonucleic acid.

From the thirty patients studied one cannot draw any dogmatic conclusion about the frequency of the different staining patterns in the various " autoimmune " diseases. Homogeneous and speckled antibodies seem to have about the same incidence. The nucleolar pattern, on the contrary, encountered only once, probably has a much lower frequency than the 1 in 30 suggested by this small series, because the appearances are so striking that they could hardly have been overlooked during the extensive examination of serum from various collagen diseases by other workers using the Coons technique.

Summary

Three patterns of " autoimmune " nuclear fluorescence have been identified in the serum of patients with Sjögren's syndrome, systemic lupus erythematosus, and other possible autoimmune diseases.

Homogeneous nuclear staining is produced by an antinuclear factor specific for deoxyribonucleoprotein. The antigen responsible for speckled nuclear staining has not yet been identified.

Nucleolar staining, which was produced by one serum specimen, possibly represents an antinuclear factor which reacts with the structural ribonucleic acid of the nucleolus.

This work was undertaken while I held a clinical research fellowship of the Medical Research Council. I am indebted to Dr. J. H. Humphrey and Dr. B. M. Balfour for advice and encouragement, to Miss Lorna Franklin for valuable technical assistance, and to Mr. M. R. Young for the photography.

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" . . . The act of driving a car is one of the few outlets available to most people for their need to exercise personal power and assert their individuality. Skill in driving and roadmanship enable the ordinary person to express his innate sense of craftsmanship, which in the modern world has too little outlet, and one by-product of this, incidentally, is more road accidents. Speedy and expert handling of motor-cars is admired and glamorised. The young have been taught to look with envy and hero-worship at the fast driver—including the too-fast driver—in a way they do not look at any other criminal, such as the safe-breaker, or the cat-burglar. . . . We only become social individuals when we step out of our cars, and I suspect that if the glamour and satisfaction derived from operating a car were transferred to something else, many people would find it more of a gain than they imagine. It is hardly a step forward in civilised living when nearly every member of a society spends more and more of his life shut up by himself in a metal box."—Prof. J. M. RICHARDS, *Listener*, May 11, 1961, p. 823.

CROHN'S DISEASE PRESENTING AS PYREXIA OF UNKNOWN ORIGIN

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FEVER is a well-known feature of regional ileitis, and is said to be present in about a third of all cases, especially those complicated by fistulæ and abscesses. Less widely appreciated is the fact that pyrexia may long precede other manifestations of the disease, and that regional ileitis may be the occult and unsuspected cause of lengthy periods of pyrexia.

When Bockus (1943) described a case of regional ileitis in which fever preceded any other symptoms by a year, he was unable to find any similar case. A year later Sprague et al. (1944) reported a case of regional ileitis, in a girl of 15, in which fever and joint pains preceded overt manifestations of abdominal illness by eight months.

In 1947 Crohn and Yarnis thought it necessary to draw attention to the fact that regional ileitis (as well as ulcerative colitis and regional colitis) could be responsible for long-continued pyrexia of unknown origin (P.U.O.), and they remarked that none of the major publications dealing with this often baffling diagnostic problem mentioned gastrointestinal disease as a possible cause. They described 2 illustrative cases:

Rheumatic fever had been diagnosed in a girl of 12 on the grounds of fever of fourteen months' duration, a raised erythrocyte-sedimentation rate (E.S.R.), anæmia, and slight leucocytosis. There had been very mild diarrhœa, but no abdominal pain. Regional ileitis was only recognised as the cause of her symptoms when a barium follow-through X-ray examination was carried out. The 2nd patient was a man of 17 who had had bouts of fever at intervals for seven years. He could recall only one transient episode of diarrhœa lasting a few weeks. Brucellosis seemed the most probable diagnosis before a barium follow-through X-ray examination showed the changes of regional ileitis.

Eleven years after the publication of these two cases the same workers (Crohn and Yarnis 1958) mentioned that in a series of 542 cases of regional ileitis, fever was the first or presenting symptom in 11; and they again stressed the importance of keeping regional ileitis in mind when investigating a case of pyrexia of unknown cause.

Yet, despite such reminders, regional ileitis is still neglected as a possible cause of P.U.O., and of seven standard textbooks of medicine recently consulted only one mentions this important point. Even the encyclopædic *Index of Differential Diagnosis* (Douthwaite 1960) fails to list regional ileitis among the 107 conditions given as possible causes of protracted fever.

Hence, we record 2 further cases of long-continued pyrexia due to occult regional ileitis.

Case-reports

Case 1.—A boy of 16 was admitted on March 7, 1957. Three months before he began to have intermittent aching in both knee-joints. Attacks affected either knee separately or both together, but there was no swelling of the affected joints. The pain was relieved by aspirin. There was associated anorexia and he lost 14 lb. within six weeks. At this time his bowels

opened once daily and stools were of normal consistence. Abdominal pain was absent. There were no abnormal physical signs, except for an evening fever of up to 100°F. This was abolished by aspirin, but recurred when the drug was discontinued. Apart from the joint pains he had no complaints throughout the seven weeks of his stay; and when for four days he passed 3–4 loose stools a day this was ignored as the number of daily bowel actions and the consistence of the stools then returned to normal. Investigation at this time showed moderate anæmia (hæmoglobin 10·7 g. per 100 ml.) and a raised E.S.R. of 64–88 mm. (Westergren) in the first hour. A total and differential white-blood count; urine analysis; Widal and brucella agglutination tests; serum plasma-protein estimation; blood-cultures; Paul-Bunnell test; electrocardiography; radiography of the chest, bones, and renal tract; electromyography; and biopsy of an axillary lymph-node gave results within normal limits.

He was then discharged (seven weeks after admission), but was readmitted five weeks later because of the onset of colicky lower-abdominal pain associated with diarrhœa, about 8 watery stools being passed daily. He had lost a further 8 lb. A barium follow-through X-ray examination was carried out and showed changes suggestive of regional ileitis. The diagnosis was confirmed by histological examination after the terminal ileum and ascending colon had been removed at operation.

Case 2.—A woman of 30 was admitted to another hospital on Sept. 11, 1958. For three weeks she had had palpitations and had felt generally unwell. A few days before admission she had had a mild and transient attack of thrombophlebitis in the right leg. On admission she had an evening fever of up to 99·2°F. A soft systolic murmur was audible at the apex, and the spleen was just palpable. Investigations at this time:

The hæmoglobin was 11·9 g. per 100 ml. Total and differential white-cell counts normal. E.S.R. 26–35 mm. in the first hour. Blood-Wassermann reaction negative. Urine analysis normal. Total plasma protein 5 g. per 100 ml. (albumin 2·4 g., globulin 2·6 g.). Serum-calcium and serum-phosphorus normal. Stool culture negative Widal and brucella agglutination tests negative. Leptospiral agglutination tests negative. Chest radiograph normal. Lupus-erythematosus-cell test negative. Blood-culture (× 6) sterile.

Electrocardiograms on Sept. 17 showed T-wave inversion in Leads III, aVf, and V 4–7. On Oct. 2 the tracings were almost normal.

Three weeks after admission it was thought that the apical systolic murmur had become rougher. A presumptive diagnosis of subacute bacterial endocarditis was made and treatment with large doses of penicillin was begun; after two weeks' therapy with penicillin, streptomycin was given in addition. There was a slight fall in the average temperature at first, and though she felt better and put on 9 lb. there were still occasional evening temperature spikes up to 99°F. She was discharged on Jan. 12, 1959.

Next year she began to complain of tiredness and lost 7 lb. Attacks of palpitations recurred, and she now had night sweats. In the evenings her temperature rose regularly to 99·2°–100·2°F. There was no change in the physical findings, but she was still slight anæmic (hæmoglobin 11·9 g. per 100 ml.) and the E.S.R. remained raised (30 mm. in the first hour). On Feb. 4, 1960, she was admitted to The London Hospital. The only new findings were a few tender nodules on the shins. Laboratory findings were unchanged; repeated blood-cultures were negative.

The diagnosis was still thought to be subacute bacterial endocarditis and a full course of penicillin was given. Treatment had no effect on the symptoms or the fever, and she continued to feel unwell and to complain of palpitations, attacks of sweating, and a new feature—left-sided headaches. From the beginning of her illness she had had a single daily motion with a firm formed stool, except for one day in hospital when she passed 4 motions. A week after penicillin was discontinued a routine re-examination revealed a tender mobile sausage-shaped mass in the right iliac fossa. The character of this mass suggested Crohn's disease, and a barium follow-through X-ray examination showed changes compatible with this diagnosis, which was confirmed histologically after resection of the affected portion of gut.

Discussion

Crohn and Yarnis (1947, 1958) have pointed out that cases of regional ileitis are often overlooked when diarrhœa and abdominal pain are absent or slight. When fever is the only or the outstanding feature, any of the more familiar causes of pyrexia may be thought to blame.

In Bockus's case (1943) subacute bacterial endocarditis was suspected, and recovery of a streptococcus from the blood seemed to confirm this diagnosis. Only after a year did abdominal pain direct attention to the bowel, and then a barium follow-through X-ray examination showed changes suggestive of advanced regional ileitis.

In the 1st of the 2 cases described in detail by Crohn and Yarnis (1947) mild diarrhœa was ignored, and after three months' investigation in hospital a diagnosis of rheumatic fever was made on the strength of fever, moderate anæmia, mild leucocytosis, and a raised E.S.R. Diagnosis was finally made by radiological examination. In the 2nd case fever had lasted for seven years, but during the whole of this time there had been only one transient period of diarrhœa for a few weeks, followed for the rest of the time by normal motions. Abdominal pain was absent throughout, and the diagnosis was eventually suggested by routine radiological examination.

In the 1st of our 2 cases the joint pains, fever, raised E.S.R., and moderate anæmia made a diagnosis of rheumatic fever reasonable, and the excellent response to aspirin strengthened the suspicion. But there was never any objective evidence of arthritis, and the significance of a transient episode of diarrhœa was not recognised.

In the second case everything pointed to subacute bacterial endocarditis, and the patient had two courses of antibacterial treatment. It was only after twenty months' continuous fever that an abdominal mass became palpable and suggested the true diagnosis, which was supported by radiological appearances and proved by operation. In retrospect, a finding which should perhaps have raised a suspicion of intestinal disease was the low plasma-albumin.

It is easy to see how, when regional ileitis is accompanied by eye changes, erythema nodosum, and joint symptoms, rheumatic fever, disseminated lupus erythematosus, or brucellosis may be reasonably suspected. If, as sometimes happens (Crohn and Yarnis 1958), there is slight eosinophilia, polyarteritis nodosa may be simulated. Likewise, an innocent heart murmur associated with fever may lead to the diagnosis of subacute bacterial endocarditis, particularly if there is also splenomegaly and finger-clubbing.

Accurate diagnosis rests upon the proper attention being paid to abdominal pain and diarrhœa, however slight or short-lived; and, even when these symptoms are absent, a barium-meal investigation is advisable in a case of P.U.O. when other tests are negative or only doubtfully positive.

We are grateful to Lord Evans and Dr. Robert Benson for permission to publish these cases.

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GRAPHIC FLUID-BALANCE CHART

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CHARTS commonly in use for recording a patient's intake and output of fluids are cumbersome and complex. Long columns containing numerous entries in differing and often illegible handwriting have to be added up at the end of a 24-hour period, and then a little sum has to be done to determine whether the patient is in balance. In any surgical ward there is always a considerable number of patients for whom such records must be kept and the daily reckoning is a tedious and time-consuming affair—so much so, that it is not uncommon to find that, though the individual entries are laboriously made by the nurses the hard-pressed resident in a busy hospital may not find the time to add them up and draw up the balance.

The chart presented here uses the graphic method to record the amount of a patient's fluid intake and output. Two columns are built up side by side on the graph paper, one representing intake and the other output. Any discrepancy is seen immediately as a difference in height between the two columns.

Figs. 1 and 2 show the front and back respectively of the chart. The strip of graph paper in the middle of the sheet is divided vertically by a double line into two columns, the left-hand column representing intake and the right-hand column output. A horizontal line divides these columns into two parts; above this line are charted fluids taken and lost by normal means—fluids given by mouth, and those lost in the urine and via the skin and lungs. Below the line are charted fluids administered and removed by other means—e.g., intravenously or by aspirate. Each small square represents 10 ml., each large square 1 litre; and an entry is made by outlining the appropriate number of squares, starting on the horizontal line and working up or down. On the assumption that the average fluid loss from the skin and lungs is a litre a day, a large square in the output column is already blocked out and the column representing urine lost is started above this. Spaces on each side of the graphed columns are used for recording the nature of the fluids and the times given, and, to assist in maintaining an electrolyte balance, space is provided for entering the sodium and potassium content of the fluids taken and lost. Notes at the bottom of the sheet give roughly the electrolyte content of urine, aspirate, fistulæ, &c.

On the reverse side of the chart are three tables. On the first the resident can enter details of the fluid to be given in the next 24 hours. The second shows the electrolyte and calorie content of standard solutions available, and the third is used

FLUIDS TO BE GIVEN

By mouth 50 ml. per hour Intravenously 2000 ml. Drip rate (litres x 12) 24 drops/min.

	Vol.	Type of Fluid	Sodium	Potassium	Calories	Initial as Given
1	500	N. Saline	4.5			A.B.
2	500	5% Dextrose			100	C.D.
3	500	N. Saline	4.5			A.B.
4	500	5% Dextrose			100	E.F.
5						
6						
7						
8						
9						
10						
11						

STANDARD SOLUTIONS AVAILABLE

Volume	Type of Fluid	Gms. NaCl	Gms. KCl	m. Eq. Na	m. Eq. Cl	m. Eq. K	m. Eq. HCO_3	Calories
500 ml.	Normal Saline	4.5	-	75	75	-	-	-
500 ml	½ Normal Saline	1.5	-	25	25	-	-	65
500 ml.	1/5 Normal Saline	1	-	15	15	-	-	80
500 ml.	5% Dextrose (+ Ethanol)	-	-	-	-	-	-	100 (250)
500 ml	Hartman's Solution	3.5	0.2	60	55	2.5	12	-
400 ml.	Plasma	4	0.5	70	35	5	30	-
500 ml.	m/6 Na Lactate	4.5		80	-	-	-	-
5 ml.	Ampoule KCl		1	-	-	13	-	-

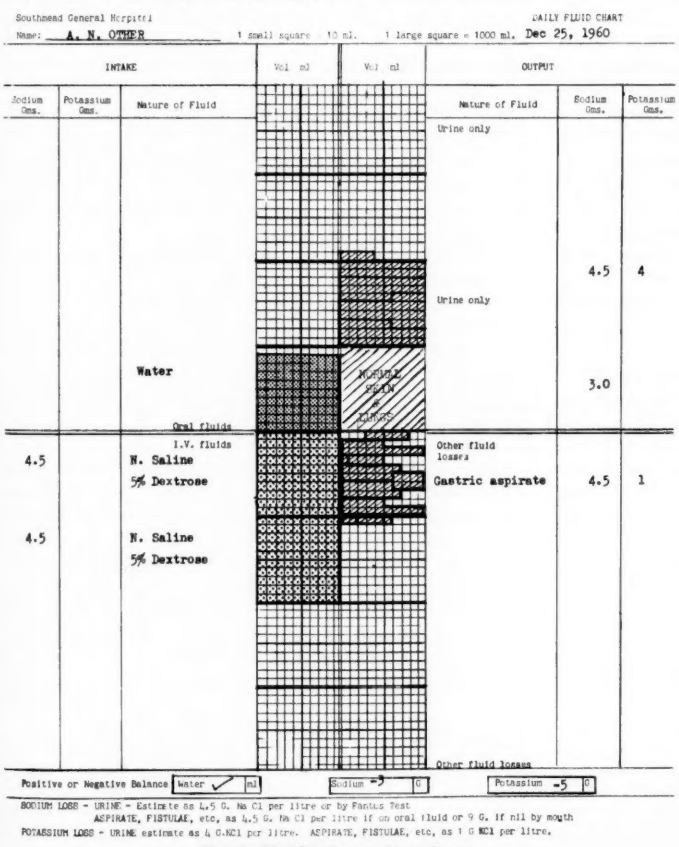
ESTIMATE OF REQUIREMENTS

Period beginning December 25 and ending December 26

	Water	Sodium	Potassium
Deficit	-		
Expected Normal Losses Lungs & Skin (1,000 ml.)	1000	3.0	
Urine (1,000 - 1,500 ml.)	1000	4.5	4.0
Expected Abnormal Losses Pyrexia 101° F or above (add 500 ml.)			
Excessive Sweat (add 1,000 ml. and 3 G. Sodium)			
Aspirate, fistulae, etc			
Urinary Losses in excess of 1,500 ml.	1000	4.5	1.0
Total Requirements	3000	12.0	5.0

1 G NaCl = 17 m.Eq. Na 1 G KCl = 13 m.Eq. K

Fig. 2—Fluid-balance chart, back.



SODIUM LOSS - URINE - Estimate as 4.5 G. Na Cl per litre or by Fantus Test
ASPIRATE, FISTULAE, etc, as 4.5 G. Na Cl per litre if on oral fluid or 9 G. if nil by mouth
POTASSIUM LOSS - URINE estimate as 4 G.KCl per litre. ASPIRATE, FISTULAE, etc, as 1 G KCl per litre.

Fig. 1—Fluid-balance chart, front.
Shading has been added for clarity.

for estimating the patient's water and electrolyte requirements. Detailed recommendations regarding the use of these tables has been given elsewhere (Tovey 1960). The sheets are the same size as the standard temperature chart and are kept at the foot of the bed on the same type of board. They are printed in red so that blue ink stands out clearly on the graph.

This chart was introduced in some of the wards at Southmead Hospital during 1959, and has been found simple and time-saving. In general, the resident and nursing staff of those wards say they prefer this graphic method of recording intake and output and would not like to return to the old system.

REFERENCE

Tovey, G. H. (1960) Technique of Fluid Balance. Edinburgh.

Preliminary Communication

A METHOD OF OBTAINING FÆCAL FLUID BY IN-VIVO DIALYSIS

NORMAL stool, despite its solid consistency, contains 70–80% of water. This fluid may conveniently be regarded as consisting of two components—one which is exchangeable with body-fluids and is under the influence of the absorptive and secretory activities of the bowel (free fluid), and a second, non-exchangeable, component, imprisoned in vegetable fibres, seeds, bacteria, &c., and relatively uninfluenced by bowel activity (bound fluid). The composition of the exchangeable component is likely to be altered by certain drugs and diseases (e.g., purgatives, mineralocorticoids, bowel diseases), and a simple method of obtaining this fluid might have some clinical value.

We have made use of the principle of dialysis to obtain samples of exchangeable fæcal fluid. Small bags of a semipermeable membrane ('Visking' cellulose tubing,* size $^{8}/_{32}$ in.) containing a watery solution of polyvinylpyrrolidone (P.V.P., mean molecular weight approx. 30,000) were swallowed, recovered from the fæces, and their contents analysed. Best results were obtained using cellulose bags 6 cm. or more in length, tied at both ends (total capacity 2 ml.) containing 150 mg. of P.V.P. in 0·5–1·0 ml. of solution.

The following considerations suggest that the contents of such bags, when recovered from the stool, are in chemical equilibrium with the exchangeable fluid component of the stool itself: (1) In-vitro experiments showed that within 2 hours the contents of bags had the same concentration of sodium, potassium, calcium, and chloride as their environment; (2) although the time taken for bags to traverse the alimentary tract varied between 24 and 120 hours, bags were shown radiologically to be in the large intestine within 3 hours of ingestion; (3) bags placed in the rectum from below and recovered after 8 hours had the same composition as bags taken by mouth and passed in the stool.

*Obtained from Hudes Merchandising Corporation, London, W.1.

TABLE II—EFFECT OF MINERALOCORTICOIDS ON THE COMPOSITION OF FÆCAL FLUID

Subject	Na (mEq./l.)	K (mEq./l.)	Na/K
Normal 1 (9αF)	2·6	105	0·025
Normal 2 (9αF)	2·4	101	0·024
Normal 3 (9αF)	1·1	111	0·009
Primary aldosteronism ..	2·6	134	0·019

9αF = 9α-fluorohydrocortisone.

The fluid obtained by this method has a brown colour and an odour similar to that of fæces. Table I shows some of the features of its composition in three normal subjects. The fluid is slightly hyperosmotic, and in-vitro experiments showed that no more than 15 mOsm. per kg. of the determined osmolality could be attributed to P.V.P. The ratio of sodium to potassium is similar to that of whole stool, and the reverse of that of small intestine contents. The high concentration of ammonium may be due to bacterial breakdown of urea, which was absent from all specimens, and this process may also have contributed to the figure for total carbon dioxide (probably mainly bicarbonate, at pH 6·9). The high and variable concentration of calcium may be partly artefact; for a light precipitate was frequently present within the bags, and analysis showed that this contained a large amount of calcium. The magnesium concentration of the fluid is even higher than that of calcium but this substance may likewise be partly precipitated. Calculation shows a distinct anion gap, presumably due to unmeasured organic anion.

The chemical composition of fæcal fluid from these cellulose bags may be compared with that of whole stool from the immediate vicinity of the same bags, and a ratio obtained indicating the diffusibility of the substance concerned. In ten experiments the mean and standard deviation of this ratio (concentration in fæcal fluid per litre of water/concentration in stool per litre of water) was for sodium $0·92 \pm 0·07$, for potassium $0·70 \pm 0·11$, for calcium $0·15 \pm 0·07$, and for total phosphorus $0·07 \pm 0·07$. Almost all the sodium in stool thus appears to be diffusible, but about a third of total stool potassium is non-diffusible, and is perhaps imprisoned in vegetable matter. By contrast stool calcium and phosphorus are very poorly diffusible, and appear to be excreted in an insoluble form—indeed even these low ratios may be misleadingly high because of trapping by precipitation of calcium and phosphate which entered the bags higher in the bowel.

Table II shows the sodium and potassium composition of fæcal fluid from three normal subjects taking 9α-fluorhydrocortisone (3 mg. per day, for 3 days) and from one patient with primary aldosteronism due to an adrenal cortical adenoma. Sodium concentrations are very much lower and potassium concentrations slightly higher than in normal subjects, with the result that Na/K ratios are well below the lowest normal figure.

TABLE I—COMPOSITION OF FÆCAL FLUID IN NORMAL SUBJECTS

—	Water content (g./ml.)	pH	Osmolality (mOsm./kg. water)	Na (mEq./l.)	K (mEq./l.)	Na/K	Ca (mEq./l.)	Mg (mEq./l.)	NH_4 (mEq./l.)	Cl (mEq./l.)	Total CO_2 (mM./l.)	Total P (mM./l.)	Urea
Mean ..	0·93‡	6·90	376	30	77	0·50	40	56	19	14	39	6·6	Nil
Range† ..	0·91–0·95	6·62–7·24	336–423	6–93	40–108	0·08–2·2	7–85	52–60	9–33	7–20	22–66	2·5–16	
No. of observations	3	10	12	22	22	22	10	2	15	13	17	4	15

† Several parameters showed a markedly skew frequency distribution, and therefore ranges of values, rather than standard deviations, are given.
‡ The high proportion of total solids is due to P.V.P.; results expressed per litre require a correction of approximately +7% to yield concentrations per litre of water.

This technique may provide a convenient means for collecting any soluble fæcal material and has the advantage that results can be expressed as concentrations per litre of fluid.

We would like to thank Miss Christine Harper and Miss Evelyn Clarkson for analytical assistance. This work was supported by a grant for technical assistance from the Medical Research Council.

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Reviews of Books

The Choice of a Medical Career

Essays on the Fields of Medicine.—Editor: JOSEPH GARLAND, M.D., SC.D.(hon.), editor, *New England Journal of Medicine*; JOSEPH STOKES III, M.D., associate in preventive medicine, Harvard Medical School. Philadelphia: J. B. Lippincott. 1961. Pp. 231. $5.

BEFORE he qualifies a medical student has many counsellors to advise him on the essentials for success in his vocation. But shortly thereafter, when he must make some far-reaching decisions about which branch of medicine he will enter and how he will prepare himself for it, he sometimes makes his choice alone, without real insight into his abilities, and without appreciating that there are different but fairly well-defined paths to distinction in the various specialties. That some doctors with close relatives already established in the profession achieve an early success is often due, not to nepotism, but to the wise advice they get about which appointment to seek.

For the young graduate in North America these problems have now been simplified by this unusual book in which twenty-two notable specialists describe their work, the type of personality most likely to accord with it, and the programme of study appropriate to it. Most of the chapters are prefaced with a brief historical note and several include a bibliography or list further sources of information. Some are predominantly factual: some, such as that on psychiatry by Prof. John Romano, are philosophical as well. Romano quotes Charcot's motto from Terence *Humani nihil a me alienum puto* (Nothing than concerns a man do I deem a matter of indifference), and it is probably this unifying concept which explains why, though it has been written by so many pens, and with reference to American legislature, this book seems neither heterogenous nor parochial. It will help postgraduates in this country almost as much as in the United States.

The Clinical Application of Antibiotics

Vol. II. *Streptomycin and other antibiotics active against tuberculosis.* M. E. FLOREY, M.D. London: Oxford University Press. 1961. Pp. 336. Price 84*s*.

MANY will be grateful to Lady Florey for this comprehensive account of the clinical applications of streptomycin and other antibiotics effective against tuberculosis—a worthy addition to her previous volumes on the scientific aspects of all important antibiotics and the clinical applications of penicillin. Though it is numbered volume II it has been preceded by volumes III (chloramphenicol and the tetracyclines) and IV (erythromycin and other antibiotics).

The active organism, *Actinomyces griseus*, was identified in the soil by Waksman in 1919, and the active antibiotic, streptomycin, was first isolated by Schatz, Bugie, and Waksman in 1944. In view of its stability and apparently low toxicity it seemed very promising, all the more so when Feldman, Hinshaw, and Moses in 1945 reported that it could suppress tuberculosis in guineapigs. But since then its reputation has suffered much. At first it was acclaimed as the ideal counterpart of penicillin which would cure all bacterial infections not cured by penicillin. But when its toxic effects on the ear and its tendency to produce drug resistance became obvious, it was judged to be suitable only for the treatment of tuberculosis. In this capacity it gradually came to play a dominant part, but later it seemed likely to be eclipsed by isoniazid. As the value of combined therapy became clear, the importance of streptomycin again received wider recognition. During the past ten years other antibiotics acting on tuberculosis have been discovered, but none of these has proved as good as streptomycin for general use.

In an account of the activity of streptomycin in vitro and its toxicity, especially on the VIII nerve, it is recommended that an intramuscular dose of 2 g. daily should very seldom be exceeded; 1 g. daily may usually be continued indefinitely without ill effects. Drug resistance is best avoided by the simultaneous administration of some other antibacterial drug—e.g., isoniazid, *p*-aminosalicylic acid, or penicillin, which will control any organisms which might become resistant to streptomycin. Resistance seems to be due to a spontaneous mutation, and it is highly unlikely that two such mutations will arise at the same time. Streptomycin is of value in the treatment of tularæmia, plague, granuloma inguinale, and chancroid, but the results with other (non-tuberculous) infections have been disappointing.

The main part of the book is about the action of streptomycin in tuberculosis; and finally Lady Florey describes other antibiotics which have been used against tuberculosis, especially kanamycin, but also viomycin, neomycin, cycloserine, and streptovaricin. At present none seems likely to replace streptomycin.

The bibliography of approximately 1900 items is selective rather than comprehensive (but surely 1900 is enough for most readers). References are given up to the end of 1959; and most of them seem to fall between 1947 and 1955. There is a short subject index of 7 pages; but there is no authors' index. The writing is clear, and the printing and form are attractive. This book will probably become the standard work on the treatment of tuberculosis with antibiotics and on the clinical applications of streptomycin, and it should be in all medical libraries.

Handbook of Abnormal Psychology

An Experimental Approach. Editor: H. J. EYSENCK, PH.D., professor of psychology, University of London; director of psychological laboratories, Institute of Psychiatry; psychologist, Maudsley and Bethlem Royal Hospitals. London: Pitman Medical Publishing Co. 1960. Pp. 816. 120*s*.

THIS massive compilation of papers by twenty doctors and psychologists from the Institute of Psychiatry and the Maudsley and Bethlem Royal Hospitals sets out Professor Eysenck's claim that psychological phenomena should be subjected to the experimental and statistical procedures of the physical sciences.

Opening with a chapter by the editor on classification and the problems of diagnosis, the first section of the book deals with the description and measurement of abnormal behaviour as it affects psychomotor functions, expressive movements, sensory perception, intellectual abilities and problem-solving behaviour, cognitive abnormalities, and abnormalities of motivation and "ego-functions". Part two is devoted to the causes and determinants of abnormal behaviour, with chapters on heredity and psychological abnormality, constitutional factors, childhood upbringing and other environmental factors, somatic reactivity, conditioning, and learning and abnormal behaviour. Part three, on the experimental study and modification of abnormal behaviour, has chapters on the psychological effects of brain damage, of psychosurgical procedures, and of cerebral electroshock. Professor Eysenck is co-author of the chapter on the effects of drugs on behaviour, and writing on the effects of psychotherapy, he elaborates his well-known criticisms of the psychotherapists who presume to treat their patients without control groups and statistical analyses of therapeutic results.

This outstanding book demonstrates that Professor Eysenck and his talented colleagues at the Institute of Psychiatry are truly more "scientific" than any other school, by virtue of the plethora of numerical measurement applied to their data. The dictum of Konrad Lorenz may serve as epilogue: "We are

living in a time when it has become fashionable to assess the 'exactitude' and, with it, the value of any scientific result exclusively by the degree to which quantifying methods took part in obtaining it. This opinion is one of the dangerous half-truths which fashion is all too prone to accept."

Neurology Simplified

DAVID JOSEPH LA FIA, M.D., assistant in neurosurgery, Jefferson Medical College and Hospital, Philadelphia. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960. Pp. 175. 54*s*.

THE object of this book is to encourage general practitioners to suspect neurological disease and make a reasonable shot at the diagnosis, thus reducing the number of patients who are referred to specialists too late. The book is in two parts: the first deals with the technique of neurological diagnosis under three headings—ætiological, anatomical, and clinical diagnosis—and the second is a systematic discussion of the commonest neurological disorders. Throughout the book the emphasis is on simplicity, and this aim has been successfully achieved. The book will also be useful to medical students.

Adolescence

The Years of Indiscretion. T. A. A. HUNTER, T.D., M.B., M.R.C.P., resident medical officer, Marlborough College, Wilts; M. E. M. HERFORD, D.S.O., M.B.E., M.C., M.D., D.P.H., appointed factory doctor, Windsor and Slough District. London: Heinemann Medical Books. 1961. Pp. 160. 15*s*.

THE authors have written for the parent, school-teacher, or youth leader who requires a simple and reasonably complete guide to whether the development of a particular child is or is not proceeding normally; and they try to provide information about the common difficulties of adolescence. " Most of the facts . . . are presented at a level where unanimity of opinion permits of dogmatism without fear of contradiction."

There is a chapter on general physical development and another on psychological development. The main sexual changes that take place at puberty are then described and nutritional needs briefly discussed. The chapter on hygiene emphasises the importance of routine to the adolescent. It is said that the best way to prevent adolescents smoking is to suggest that the development of an expensive habit may be a considerable handicap when the time comes to marry and assume financial burdens. Much importance is placed on the health of mind and body that comes from sports, games, and physical education.

Adults often find it very hard to help the adolescent with his problems or even to discuss them in language he understands. Such enormous problems exist—social, psychological, sexual, and spiritual—that Dr. Hunter and Dr. Herford may seem to have planned their book with too much emphasis on the physical aspects; but to the lay audience they are addressing they have guidance to offer on many topics.

Techniques of Thoracotomy

B. T. LE ROUX, M.B., F.R.C.S.E., senior registrar, Regional Thoracic Unit, Edinburgh. Edinburgh: E. & S. Livingstone. 1961. Pp. 94. 55*s*.

CONFINING himself solely to the surgery of access to the thoracic cavity for all types of pulmonary, œsophageal, and cardiac operations, the author describes in great detail how these procedures are carried out in his own unit; and he has firmly avoided confusing the issue by describing the many variants in use, though major alternatives might perhaps have been given a hearing. A thoracic surgeon in training will be able to learn from this book how to do a thoracotomy, provided, of course, he also gets practical guidance in the operating-theatre; and the book will also be of great use to general surgeons unused to thoracotomies who may have to do them occasionally.

The vertical sternum-splitting incision for cardiac operations is (contrary to the author's statement) probably the commonest now for cardiopulmonary bypass and hypothermia, whereas the bilateral anterior transternal thoracotomy is falling out of favour unless the operation planned makes it a necessity. Drainage of the vertical incision is described for thymectomy but not adequately for cardiac surgery and particularly bypass surgery. The chapter on thoracoplasty incisions should describe the removal of the first rib, for while this may not be done in Edinburgh it certainly still is elsewhere, and guidance is needed in this the most difficult and dangerous part of the operation. The chapter on drainage of an empyema thoracis is a model account of the technique but again a short section on the drainage of a subphrenic abscess might have been valuable because this may often come the thoracic surgeon's way.

The book is beautifully printed and the illustrations and colour plates are excellent, but it seems a mistake to photograph the white towels with blood on them (as the author deliberately decided to do) because in many of the beautiful colour photographs the contrast between tissues and towels is diminished. Nevertheless the author is to be congratulated on such a readable and instructive book on this vital part of thoracic surgery.

The Protection of the Nurse Against Tuberculosis

F. A. H. SIMMONDS, M.A., M.D., D.P.H., physician and medical director, Clare Hall Hospital, Middlesex. London: The Chest and Heart Association. 1960. Pp. 86. 12*s*. 6*d*.

THIS little book, by a physician with long experience in chest-hospital work, can be strongly recommended. It deals lucidly and simply with the protection of the health of nurses in contact with tuberculous patients. It should be of particular value in training doctors and nursing instructors in the less fortunate countries where tuberculosis is still a big problem; but those in general hospitals in this country can also learn much from it.

Dunham's Premature Infants (3rd ed. New York: Paul B. Hoeber. 1961. Pp. 578. $15).—It is sad that Dr. Ethel Dunham has relinquished the authorship of this well-regarded work which, from the first edition in 1948, has brilliantly fulfilled the aim to provide " a source of information in regard to prematurity and a guide for the general care of the premature infant ". Dr. William A. Silverman has proved an able successor and while he has wisely left the arrangement and organisation of the book unchanged, he has brought it up to date and imprinted many of his own attitudes. He is insistent that practices in the care of the premature infant should be rigorously scrutinised and subjected as far as possible to controlled clinical trial. He has little use for clinical impressions and authoritative statements, and abhors the uncritical use of treatments that may be toxic and are of dubious benefit. In spite of the increases in knowledge of the past decade (reflected by 100 pages more in this book) much of the care of the premature remains empirical. In these circumstances Dr. Silverman does not hesitate to tell us what he and his colleagues do, thereby maintaining the practical value of the book. It may be questioned whether much of the statistical and epidemiological data are of immediate relevance. They are here presented in an interesting way, but coming from American sources they are of only comparative value to the British pædiatrician. And some of the techniques and apparatus advocated might have to be modified for use in Britain. This very useful book is well produced and easy to read; and the charts and diagrams are cleverly drawn and excellently printed.

Specifications for Pesticides (*Insecticides—Rodenticides—Molluscicides—Herbicides—Auxiliary Chemicals—Spraying and Dusting Apparatus*. Geneva: World Health Organisation. 1961. Pp. 523. Obtainable from H.M. Stationery Office, P.O. Box 569, London, S.E.1. 50*s*.).—This technical manual deals with all the substances in common use which fall into the categories listed in the title. For each it gives the description, the chemical and physical properties, and the correct labelling, followed by a detailed description of the methods suitable for its analysis. It does not catalogue all the trade names under which a substance is sold nor does it deal with fungicides. The notes on toxicity are brief and limited to the effects on humans.

THE LANCET

LONDON 3 JUNE 1961

First Things First for the Injured

THOUGHT about chest injuries came almost to a standstill after the late war, for many felt that the last word on their management had been written. But the forms of treatment that had proved their worth in battle casualties chiefly concerned penetrating wounds: interest was focused on hæmothorax, pneumothorax, lung wounds, and particularly traumatic empyema. In civilian practice these are complications that demand correction but are seldom in themselves urgent threats to life. The emphasis has latterly been more on accidents due to acceleration and deceleration whose general effect is to crush and to burst viscera and blood-vessels rather than to penetrate them. Unfortunately, HOLMES SELLORS [1] is right in saying that " it has not been fully appreciated how many people die untreated from injuries to the chest, and in many cases the damage is only recognised after death".

On the clinical side, interest is now concentrated on the maintenance of efficient respiration, and higher precedence is being given to dangerous chest injuries because it is recognised that, as soon as a patient stops ventilating his lungs, his heart and brain will die. Young people, who are particularly liable to serious chest injuries, show remarkable resilience provided lung function can be restored soon after an accident. Indeed many have been saved though their injuries were at first sight such that death seemed inevitable.

The particular type of injury that has made surgeons think again is " stove-in chest ". This is a usual result of head-on collisons and of accidents in which the chest is crushed, and in its serious forms it produces, initially, the same mechanical difficulties as open pneumothorax. To treat it the surgeon must appreciate the relative advantages of fixing broken ribs (either operatively or with local plaster strapping) or of stabilising respiration by means of tracheostomy, supplemented by artificial respiration where necessary, as discussed by BARRETT.[2] What kills these patients is loosely called " wet lung "—formerly regarded as " bronchopneumonia " of unknown cause but now known to precede pneumonia and cause it. A possible complication of any chest injury, wet lung implies an excess of liquid in the air-passages. This may be blood, saliva, or vomit that has been inhaled; but equally it may be the result of pulmonary œdema, or an excess of bronchial secretions. Wet lung may drown a patient within an hour of an accident, or it may develop insidiously at any time. It is encouraged by morphine or any drugs that depress cough or ciliary action, and it is aggravated by pain and bronchospasm. Once established, it leads inevitably to three things that may be lethal—anoxia, carbon-dioxide retention, and bronchopneumonia.

It has been found that some who have a serious chest injury, resulting in respiratory inefficiency, may be saved by tracheostomy, bronchial aspiration, and controlled artificial respiration. (This is new: not long ago the idea that respiration could be artificially controlled, in accident cases, had not been applied in practice.) The necessary emergency treatment was detailed by BARRETT, and the long-drawn-out battle in complicated cases is described in an excellent paper by WINDSOR and DWYER.[3] At a meeting of the Society of Thoracic Surgeons last November, WINDSOR pointed out that patients who have serious chest injuries cannot live unless special arrangements are made for treating them. This may mean that such cases should be moved to accident centres as soon as emergency treatment, to ensure continued respiration, has been instituted.

Special facilities, of the type here envisaged, have not yet been accepted as a part of an accident service, but they are needed not only for serious chest injuries but also for cardiac, renal, or neurological failure, and for shock and fluid imbalance. Ought we not, in fact, to develop " resuscitation units " as an integral part of accident departments? They would be equipped and staffed to prevent death in any patient who has had an injury and who reaches hospital alive—i.e., they would handle all types of physiological failure—and the treatment of individual injuries would be postponed until there was reason to think that the patient could survive. Though such units would be expensive in personnel and equipment, they would save valuable young lives. Moreover their work would permit needful clinical research, and train doctors in techniques that demand accurate and prompt action.

Detection of Lung Cancer

PERIODIC radiographic examination is a possible means of obtaining earlier detection of bronchial carcinoma. In 1951 the Philadelphia pulmonary neoplasm research project [4] was begun " primarily to study the natural history of lung cancer with special emphasis on the chronological relationship between symptoms and roentgenographic changes ". From Dec. 4, 1951, to Dec. 4, 1955, every man 45 years of age or older who presented himself for a check X-ray at the central unit of the Philadelphia Tuberculosis Health Association was invited to join the project and report twice a year for 70 mm. chest photofluorograms and questioning about symptoms. Of 6137 volunteers 66 had visible lung cancer at the time of entry (though in 10 this was diagnosed only retrospectively after a subsequent X-ray) and in 26 " new " cancer was diagnosed during the follow-up period of from three and a half to seven and a half years—an incidence of 1 per 1000 per year. Only 15 of these 26 had attended frequently enough for the natural history of their tumours

1. Sellors, T. H. *Thorax*, 1961, **16**, 1.
2. Barrett, N. R. *Lancet*, 1960, i, 293.
3. Windsor, H., Dwyer, B. *Thorax*, 1961, **16**, 3.
4. Boucot, K. R., Cooper, D. A., Weiss, W. *Ann. intern. Med.* 1961, **54**, 633.

to be defined with reasonable accuracy, and of these only 8 had been truly asymptomatic with no evidence of cancer on retrospective review; 1 of these had asbestosis and 1 minimal tuberculosis, leaving a residue of 6 " uncomplicated " cases for individual analysis.

It might have been expected that after this drastic pruning good results would have been forthcoming; but only 1 of the 6 came to thoracotomy, and all are dead; 5 of the 6 died within eighteen months after a truly " negative " X-ray. This sad record is partly offset by the information that of the total of 26 men with " new " cancers 2 others underwent resection and were still alive after two and a half years; both had squamous-cell tumours. But such a disappointing tally after approximately 60,000 individual exposures raises the question whether periodic radiographic surveys of this type are worth while.

Clearly the idea that six-monthly X-ray examination will produce a steady yield of early, operable cancers is too sanguine. Growths situated centrally behave differently from those in the periphery, and may produce collapse of a segment or lobe with subsequent infection a few weeks after an X-ray has revealed no abnormality. Sometimes a pleural effusion is the first indication that anything is amiss, and again an X-ray taken just before may be completely clear. Sometimes, too, the initial manifestation appears outside the chest altogether—with a secondary deposit in, for example, bone, lymph-node, or brain—without radiological evidence of a lesion in the chest. The chief factor determining resectability and ultimate prognosis seems to be the histological type: a slow-growing peripheral carcinoma of the squamous-cell type can be missed over a period and still prove operable. Moreover human factors are important. Tiny growths are easily missed, though retrospectively they may be readily detected; this is particularly likely in the presence of other lesions—e.g., healed tuberculous foci, where a small new shadow may be overlooked or, if it is noticed, attributed to reactivation of the original disease. Sometimes, when a small lesion is discovered, a patient who feels perfectly well will not readily accept the idea of stopping work and entering hospital for a major operation; nor is it always easy for the clinician to decide at what point this should be recommended. Finally, many patients will not find it convenient to attend regularly for X-ray, or managements may not desire the mass-radiography unit to attend quite so frequently as every six months. Even so, despite these difficulties the value of periodic radiographic examination of men aged 45 and over must be assessed, and further evidence is required before a final conclusion is reached as to its efficacy. In this country the incidence of lung cancer is higher than in the United States, and results might conceivably be better.

In a previous investigation BOUCOT and SOKOLOFF [5] found that of 29 patients with bronchial carcinoma for whom earlier films (read as negative) were available 16 had lesions which had been missed; but the fate of the " erroneous negatives " was better than that of the " true negatives ", suggesting once more that prognosis is primarily related to the rate of growth of the lesion—or, more accurately, to its degree of malignancy.

In this country BRETT [6] has shown that routine radiography of apparently healthy men (" unselective " radiography), using a mobile unit, resulted in a higher rate of resectability than routine radiography at a static unit where most of the patients were referred by general practitioners because they had respiratory symptoms (" selective " radiography). The five-year survival-rate after resection was also somewhat higher in those from the mobile unit. Possibly here there is a slight glimmer of hope; but BOUCOT and her colleagues found that radiological change does not necessarily precede symptoms. Of 15 new lung-cancer patients in their series " in whom the natural history of the disease could be accurately delineated " only 3 had X-ray changes before symptoms; 2 had concurrent symptoms, and in 10 symptoms antedated X-ray change. This sounds more alarming than perhaps it is, for there was no control series and in some patients the symptoms, although respiratory, were probably not due to the cancer which later became visible; also the record of symptoms was based on answers to questions put by clerks. Nevertheless, in some cases symptoms such as chest pain and hæmoptysis do precede visible radiographic change, and this adds another confusing element.

What we can hold on to in this complexity is that lung cancer is increasingly common among men over 45; that it may be present with or without symptoms; that a radiograph will reveal it in most instances; and that cough, chest pain, or staining of the sputum, particularly when persistent and/or associated with loss of weight, need to be investigated thoroughly, and preferably at once, even although in a large proportion of those with lung cancer it will already be too late.

The Birmingham Venture

MANY people have been attracted by the possibilities of a " balanced hospital community " as the basis for planning hospital services. The original proposals made by MCKEOWN [7] had essentially four features: the care of all types of patients at a common site; a centre consisting of multiple buildings of varied design; a common staff; and an intimate relation between hospital and domiciliary medical services. Such a centre, it was suggested, would have considerable advantages in flexibility, economy, and staffing, and when integrated closely with community services would offer perhaps the best means of assembling the complex resources on which the preservation of health depends.

Recent developments at Lancaster Moor [8] have shown that some of the advantages of this scheme can be realised in existing hospitals. Nevertheless, since adaptation of design of buildings to the needs of patients is a central feature of the proposals, their full realisation clearly requires sites where there can be a considerable

5. Boucot, K. R., Sokoloff, M. R. *Dis. Chest*, 1955, **27**, 369.

6. Brett, G. Z. *Tubercle*, 1959, **40**, 192.
7. McKeown, T. *Lancet*, 1958, i, 701.
8. Smith, S., Gibb, G. M., Martin, A. A. *ibid.* 1960, ii, 592.

amount of new building. In recent years there have been few such opportunities in Great Britain. Moreover the concept departs so radically from the traditional pattern that it would be difficult for a hospital authority to adopt it fully without more information than has so far been available.

In the hope of providing this information, the board of governors of the United Birmingham Hospitals, in cooperation with the regional hospital board and university, have embarked on the preparation of a plan for the teaching centre. Birmingham is fortunate in having sixty acres of undeveloped land beside the Queen Elizabeth Hospital and Medical School. On this site are to be planned all the institutional services for a population of approximately 100,000 living in the area around the centre. The research for the project is being undertaken jointly by the department of architecture at University College, under Prof. LLEWELYN DAVIES, and the department of social medicine, under Professor MCKEOWN; it is supported by a grant from the Nuffield Provincial Hospitals Trust.

The first object of the plan is to describe the services and to demonstrate in model form the type and layout of buildings which result from applying the concept of a balanced hospital community to a defined population. Since the site already contains a large general hospital, the main units which must be added are for mental illness, geriatrics, pædiatrics, and obstetrics. The service is to be truly comprehensive, including the acute, rehabilitative, and static phases of illness as well as outpatient and day care. The hope is that, by linking the various units with a common staff, the artificial distinction between acute and chronic illness can be broken down, and the standard of care of the mentally ill and aged sick can be raised to a level commensurate with their needs. A second object is to bring about a more intimate relationship of hospital and other medical services. Though it is widely recognised that there are serious disadvantages in the administrative separation of preventive from curative medicine and of domiciliary from institutional care, it is not easy to see how unification of services can be brought about. Major legislative changes can scarcely be introduced without experience of an improved pattern of service; yet without legislative authority such experience is difficult to obtain. In the Birmingham scheme this difficulty can, we hope, be overcome by cooperation between hospital, general practitioners, and local authority. The intention is to create a framework within which an integrated service can evolve without the impediment of traditional restrictions.

To some it will come as a surprise that such a plan should be undertaken by a teaching hospital. Teaching centres have not hitherto identified themselves with the wider problems of the medical services, and some teachers would be prepared to argue strongly that they ought not to do so. MCKEOWN [9] has suggested three reasons for this development. In the first place, since teaching hospitals have at their disposal some of the best brains in medicine, it seems right that they should put themselves into the forefront of thought about the future of its services—which they cannot do if their work is restricted to selected patients and to institutional care. Secondly, the demonstration of a balanced view of the problems confronting medicine and of the means at its disposal for solving them should be an essential component of medical education. And finally, for many research purposes access to representative patients drawn from a known population is indispensable.

Those concerned with the Birmingham scheme believe that the new responsibility can be accepted without prejudice to traditional interests. This can be done by making the size of the defined area, for which a comprehensive responsibility is taken, such that numbers of representative patients derived from it are reasonable in relation to numbers of selected patients drawn from a much wider area for other research purposes.

For our part, we regard MCKEOWN's concept of future hospitals as both sensible and promising: indeed we find it increasingly difficult to think of hospital development in other terms. We are very glad indeed, therefore, that the time has come for starting an experiment.

9. McKeown, T. Medical Services and Medical Education. Report of the Eighth Teaching Institute. (In the press.)

Annotations

ANTICOAGULANTS IN CEREBROVASCULAR DISEASE

A FEW years ago it was estimated that 70,000 people in this country were suffering from a stroke or its after-effects.[1] In the treatment of cerebrovascular disorders the early high hopes centred on anticoagulants have not been sustained by controlled studies. The history of anticoagulant therapy in cerebrovascular disease dates from more than twenty years ago, when it was suggested that heparin was of value in cerebral thrombosis and ischæmia.[2–4] Somewhat later, Rose [5] concluded that anticoagulants were of no real value in cerebral infarction; and even then the difficulty of assessment was appreciated.[6] Moreover, deaths from cerebral hæmorrhage were recorded in association with such therapy.[7 8] Brain,[9] although recognising the place of anticoagulants in the prevention of cerebral embolism, emphasised the risk of cerebral hæmorrhage and the difficulty of distinguishing between thrombosis and hæmorrhage in cases of stroke.

Bruetsch [10] found no evidence of true thrombosis in many brains with arteriosclerotic encephalomalacia; and it was realised that the natural history of cerebral vascular disease had been insufficiently studied.[11] In this country caution limited the use of anticoagulants in cerebral vascular disease [12 13]; and experimental studies in the U.S.A. appeared to indicate that after cerebral infarction

1. Glynn, A. A. *Brit. med. J.* 1956, i, 1216.
2. Magnusson, J. H. *Lancet*, 1938, i, 666.
3. Hedenius, P. *Acta med. scand.* 1941, **107**, 170.
4. Denber, H. C. B. *Schweiz. med. Wschr.* 1945, **75**, 192.
5. Rose, W. M. *Med. J. Aust.* 1950, i, 503.
6. Fisher, M. *Arch. Neurol. Psychiat.* 1951, **65**, 346.
7. McMillan, R. L., Brown, K. W. G. *Canad. med. Ass. J.* 1953, **69**, 279.
8. Wright, I. S., McDevitt, E. *Ann. intern. Med.* 1954, **41**, 682.
9. Brain, W. R. *Lancet*, 1954, ii, 831.
10. Bruetsch, W. I. *Circulation*, 1955, **11**, 909.
11. Millikin, C. H., Siekert, R. G., Shick, R. M. *Proc. Mayo Clin.* 1955, **30**, 116.
12. Elkington, J. St. C. *Brit. med. J.* 1955, ii, 1199.
13. Symonds, C. P. *Practitioner*, 1956, **176**, 130.

the danger of hæmorrhage due to administration of anticoagulants was very real.[14 15]

Nevertheless some advocated this treatment in cerebral thrombosis [16 17]; and in thromboembolic episodes its value seems certain.[18 19] But Vastola and Frugh [20] and Marshall and Shaw [21] concluded that the rate and degree of recovery from a recent occlusive cerebral vascular lesion, and its clinical course, were in no way more favourable with anticoagulant therapy than with supportive measures.

Bradford Hill et al.,[22] who have conducted a well-controlled trial of anticoagulants in chronic cerebrovascular disease, point out that the assessment of therapy is still sorely handicapped by ignorance of fundamental aspects of the disease. The pathological diagnosis teases the clinician, and in any case the definition of " effective anticoagulation " is debatable. Half their patients were treated with anticoagulants in full dosage, and half were given ineffective doses of phenindione. The incidence of non-fatal cerebral vascular accidents did not differ between the two groups. Anticoagulant therapy was found to yield no benefits and to have considerable hazards.

Barham Carter [23] still holds a moderately hopeful view of anticoagulant treatment in " ingravescent infarction ". A controlled trial on patients with non-embolic cerebral infarction with gradual onset revealed that significantly good results were obtained only in patients whose lesions were incomplete at the beginning of treatment.

It is probably reasonable to administer anticoagulants prophylactically in cardiovascular embolic disease and in atheromatous disease of the caroticovertebral system. They may also be used in selected cases of ingravescent cerebral infarction. The treatment is unlikely to be effective either therapeutically or prophylactically in chronic cerebrovascular thrombosis or in established " strokes ". Anticoagulants may be dangerous in recent cerebral embolism, and in recent cerebral infarction when cerebral hæmorrhage cannot be reasonably excluded. There are other contraindications, including arterial aneurysm, angiomatous malformation, hæmorrhagic disease, renal disease, liver disease, pregnancy, and coma. This treatment should also be avoided in cases where salicylates are being administered, and where the patient cannot cooperate or attend for the control of treatment.

DRINKING-WATER

AN ample supply of wholesome drinking-water has probably prevented more disease than any drug in the *Pharmacopœia*. International standards of purity were suggested by the World Health Organisation in 1958, but for many citizens of the world these must remain a distant goal. A new publication from the same source suggests standards applicable to Europe only.[24]

It is hard to fault. There is sufficient technical detail (supported by ample references) for the specialist reader. The frequency of sampling is discussed rationally and imaginatively. Above all there is a lucid exposition of the general principles which must govern the provision of pure water. Expert knowledge of the origin and distribution of the supply is of over-riding importance. Neither bacteriological nor chemical tests are enough by themselves, and these may, in fact, be misleading. A simple test often repeated is of more value than a more accurate and elaborate one performed infrequently. It is not enough to test the water: faults must be explained and corrected as soon as possible.

We pride ourselves on our water supplies, but far too many inhabitants of Great Britain still drink water which would be classed as unsatisfactory in any part of the world. Too many supplies are sampled and tested infrequently or irregularly or without intelligence. Too much faith is put in a single bacteriological examination. The same is true of many other parts of Europe. The professional hygienist may not learn much that is new from this booklet; but we do not know of a better introduction to the subject for the politician, national or local. The provision of pure water is their responsibility, and if they find the subject boring they ought to witness the enthusiasm and excitement of a Balkan village which has exchanged ancient wells and cisterns for clean water from the tap.

CARDIOMYOPATHY

CARDIOMYOPATHY [1] is a fashionable term which is being used to describe an increasing number of myocardial disorders. Goodwin et al.[2] have defined it as " a subacute or chronic disorder of heart muscle of unknown or obscure ætiology, often with associated endocardial, and sometimes with pericardial involvement, but not atherosclerotic in origin ". This term is most clearly applicable to myocardial abnormalities associated with the heredofamilial muscular dystrophies and ataxias,[3-5] and to some instances of familial cardiomegaly which may be variants of these generalised disorders. In the cardiomyopathies cardiac hypertrophy varies from moderate (500 g.) to colossal (1980 g.),[6] sometimes predominantly affecting one ventricle; obstruction to the left or right outflow or inflow tracts has been suggested as the cause of a proportion of these obscure cases.[2 7 8] One form of mechanical obstruction is the subaortic stenosis [8] described by Keith [9 10] and reviewed lately by Brachfeld and Gorlin [8]; but Goodwin believes that a bulging hypertrophied septum resembling Bernheim's syndrome [11] accounts for many cases of this type. Hypertrophy of the septum [7] is commonly found as a part of generalised cardiac hypertrophy, and with it's familial incidence even this variety of cardiomyopathy may not differ essentially from the many published series of familial cardiomegaly and " idiopathic cardiac hypertrophy ". Reports of the latter abound in the pre-war literature [12-16] and have often escaped notice.

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The relationship of cardiac muscular hypertrophy to interstitial fibrosis was reviewed by Fishberg,[17] who concluded that " cardiac hypertrophy is not necessarily accompanied by any considerable hyperplasia of interstitial connective tissue, but that the latter process is rather correlated with dilatation ". Brigden [1] suggested that following damage to the cardiac muscle " hypertrophy is a nonspecific response of the surviving muscle to normal hæmodynamics ". As early as 1903 Allbrecht [18] named parenchymatous inflammation of the myocardium as a cause of " idiopathic hypertrophy".

Several infectious agents have now been identified in myocarditis; they include *Trypanosoma cruzi* [19] causing cardiomyopathy as a late sequel (Chagas' disease), and toxoplasma, known to cause severe acute myocarditis. It has been suggested [20] that some examples of chronic cardiomegaly may arise as a sequel to toxoplasmosis. It is widely—but, as Cathie [21] showed, mistakenly—believed that low serological titres necessarily exclude toxoplasmosis; and neither does failure to find microscopic evidence of the disease (for example, Gilmore et al.[22] found only 3 pseudocysts in 220 serial sections of myocardium). Besides the protozoa, the Coxsackie and influenza viruses, tubercle and diphtheria bacilli, *Pasteurella tularensis*, and *Trichinella spiralis* have been incriminated as causes of myocarditis.

Whitfield [23] gives a detailed and up-to-date review, especially of familial cardiomegaly. He describes a family in which ten members were certainly affected, and six more probably, and he observes that transmission occurred only through affected females, a similar finding to previous reports. But work shortly to be published gives evidence of two families where the disease was transmitted through an affected male.[24] Whitfield again draws attention to the hazard of pregnancy and puerperium for women with cardiomyopathy.[25-28]

Vacuolation of the hypertrophied myocardial fibres has been noted in most recorded series of familial cardiomegaly and " idiopathic hypertrophy ", but it has yet to be determined whether this is an essential feature indicating hereditary metabolic defect, or merely a secondary degeneration. Excess glycogen has been found in the vacuoles and elsewhere,[1 29] but this observation has not been confirmed, though Bouin's fixative, necessary for glycogen preservation, has probably not been used sufficiently.

Battersby and Glenner [30] report non-metachromatic diastase-resistant polysaccharide in many myocardial fibres in their recent series, and they believe the evidence favours a hereditary metabolic defect of the myocardium.

The gross endocardial involvement found in African endomyocardial fibrosis is not met with in the cardiomyopathies of Europe or the Western hemisphere. This seems to be a distinct form; but Abrahams [31] has suggested that it may arise as a result of conditioning factors distorting the manifestations of recognised diseases such as acute rheumatism.

Support is badly needed for a coordinated inquiry into the many unanswered questions concerning African and South American cardiomyopathy—an inquiry which might incidentally uncover some of the answers to lesser problems elsewhere in the world.

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THE STRUCTURE OF AMYLOID

By ordinary light microscopy amyloid appears quite structureless and could justifiably be classified as one of the varieties of connective-tissue hyaline. This was originally described by von Recklinghausen [32] as glassy, transparent, structureless, refractile material composed of protein. Amyloid, however, because of its peculiar staining reactions, was for many years regarded as consisting largely of polysaccharide; and because of the frequency with which amyloidosis appeared in patients with chronic suppuration of bone and joints, chondroitin sulphate was regarded as its main constituent.[33] This was rendered extremely unlikely by Hansenn,[34] who isolated a specimen of amyloid and found that it was entirely free from chondroitin sulphate. Since amyloid is resistant to the action of testicular hyaluronidase, and the hexosamine obtained from it has been identified as glucosamine,[35] the presence of chondroitin sulphate may be definitely excluded.

The predominantly protein nature of amyloid was clearly established by Hass,[36] who found that the polysaccharide moiety did not exceed 1·5%. Of the remainder, which is almost entirely protein, remarkably little is known except that its topical activity in polarised light indicates an organised micellar structure. Recent examination by the electron microscope [37] has further revealed that amyloid consists of extremely fine fibrils of 100Å mean diameter and 3600Å mean length. They are closely interwoven and densely packed, although in places the fibrils show a parallel arrangement. This fibrillar structure has been found both in the experimentally induced deposits in animals and in naturally occurring deposits in man.

Although in most situations in which amyloid is found there is little to indicate the source of the abnormal material, in the spleen an intimate association has been observed between amyloid and plasma cells. Thus, in mice receiving multiple injections of casein for the production of experimental amyloid, the spleen undergoes considerable enlargement owing to a striking increase of plasma cells. Under the electron microscope many of these plasma cells show conspicuous vacuoles in the endoplasmic reticulum and the apparent discharge of their contents by rupture through the surface of the cell into the adjacent fibrillar amyloid.[37] A similar relationship of plasma cells, secretory vacuoles, and amyloid has also been seen in secondary amyloid in man. Presumably in those sites in which amyloid occurs remote from plasma cells, the secretion of these

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cells is transported via the blood-stream and is precipitated as it leaves the capillaries. The raised level of serum-globulin, commented on many years ago by Letterer [38] and since confirmed by many observers, may be regarded as evidence of this increased secretory activity by the plasma cells.

The mechanism by which pre-amyloid material, presumably circulating in the blood, is converted to highly insoluble enzyme-resistant material in the pericapillary tissue is still unknown. Loeschke [39] regarded the process as a form of immune precipitation between an antigen and an antibody, but there is little factual support for such a hypothesis. Letterer et al.[37] have, however, recently made use of a fluorescent rabbit anti-guineapig-complement serum to demonstrate the presence of complement in amyloid deposits, and claim that since antigen-antibody complexes fix complement the presence of complement is evidence of the presence of such complexes. This, of course, is a non sequitur and many substances other than antigen-antibody complexes are known that are capable of fixing complement. Perhaps the most important in this context is isolated gamma-globulin, especially when partly denatured by heat.

It is evident that despite a considerable reawakening of interest in amyloidosis the essential features of its pathogenesis are unknown. The available evidence would support the view that it is a form of dysproteinæmia, due to an excessive or distorted function of plasma cells, and that the characteristic amyloid material is the result of a precipitation of the abnormal protein following its interaction with the extravascular environment. If, as the electron microscope has shown, amyloid is essentially a fibrillar material the precipitation process would necessitate a conversion from a globular to a fibrous protein. Such a transformation is not unknown in protein chemistry.[40]

"NOR SO WIDE AS A CHURCH DOOR"

CRANIAL structures are highly resistant to pyogenic organisms, and reasonable preventive procedures are effective against infection following head injury; but their omission may lead to disaster. Shaving round scalp wounds, excision and debridement, and examination in good conditions by a reasonably experienced surgeon represent the minimum screening to ensure that compound fracture or penetration of the brain is not missed. The more serious forms of external wound demand full surgical facilities for removal of indriven foreign material and bone fragments.

Cranial trauma involving the ear or nasal sinuses represents a more difficult problem. A fistula into one of these cavities may require closure by a definitive neurosurgical operation. Cerebrospinal-fluid (C.S.F.) otorrhœa or rhinorrhœa in itself is not generally regarded as sufficient ground for operation unless it persists for, say, five to seven days. But the fistula may become plugged by arachnoid membrane or by protruding of brain and yet remain dangerous as a portal of entry for infection at any time.

Dinning et al.,[41] reporting on 24 cases treated by operative repair, suggest that aerocœle or an attack of meningitis are mandatory indications for operation. Signs constituting strong presumptive evidence of fistula include significant fracture in the walls of the nasal sinuses. The frontal sinus, they say, is easily shown in standard radiographic views, but ethmoidal sinuses are difficult to depict even with the aid of special views and tomography. Dinning et al. remarked that damage to this area was confirmed by unilateral rhinorrhœa or anosmia. Sphenoidal fracture was more easily demonstrated: a fluid level might be present in the sphenoidal sinus, and, although olfaction might be intact, C.S.F. rhinorrhœa was liable to be profuse and bilateral but intermittent.[42] Factors which suggested a fistula were a large defect in the wall of a sinus, separation of the edges of a fissure, and projection of a spicule of bone into either a sinus or the cranium. Since a fistula, even were it temporarily closed by cerebral tissue, carried a high risk of future intracranial infection, surgical repair should be undertaken unless the patient is unfit for a major operation.

With C.S.F. otorrhœa, or rhinorrhœa from petrous fractures with passage down the eustachian tube, a less aggressive approach was found to be justified. In nearly all such cases the discharge of C.S.F. ceased with conservative management; but in the few with persistent otorrhœa operation was regarded as justified. The difficulty in determining whether the fistula was in the middle or posterior fossa [43 44] might necessitate double exploration. Ghouralal et al.[45] successfully demonstrated such a fistula with contrast medium; this can be a useful method, but intracranial fistula in any situation may be hard to detect.

Although chemotherapy and antibiotics have transformed this branch of surgery, in common with others, they have not abolished the necessity for careful surgical work and prophylactic operation when required.[46] Natural healing of a craniopharyngeal fistula is apt to be dangerously incomplete.

A NEW CONTEMPORARY

"THERE are so many things to do; some we *have* to do; others we *want* to do; and not enough time in which to do them all." This cry from the heart is uttered by Dr. O. H. Wangensteen in an editorial introducing a new journal. The journal which Dr. Wangensteen presents to us is a monument to the triumph of some over the pressing needs of the moment. It is the *Journal of Surgical Research*,[47] and its appearance is an indication of the need for an outlet for the very considerable volume of surgical research work. Its appearance is also both a sign of the times and an act of faith—a sign of the trend towards scientific and technological adjustments within surgery, and an indication of faith that the peculiar admixture of craft, art, and technology that is surgery can be infused with new dynamism by related techniques.

That this new publication will flourish there can be no doubt. Let us hope that no surgeon in this country, wherever he may work, will consider it beyond his ken simply because it deals with research. Research must be given a higher place, and the unusual case a lower one, if surgery is to retain its position beside the other sciences. We welcome the journal not only for what it will impart but also for what it represents.

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Public Health

ANTIBODY TO POLIOVIRUS IN A WELL-IMMUNISED COMMUNITY

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IN the summer of 1960 an immunological survey was made in County Down, Northern Ireland, to find out what proportion of children had neutralising antibody to each of the three types of poliovirus. The object of the survey was, firstly, to provide information on whether a fourth dose of inactivated poliovirus vaccine was necessary and, secondly, to obtain some index of the immune status of the child population which might be of value in future comparative studies.

It is now generally accepted that three suitably spaced doses of inactivated vaccine, of the potency used in the United Kingdom, will confer about 90% protection against paralytic poliomyelitis. We subscribe to the view that this failure of complete protection reflects the inability of the vaccines to produce durable protective levels of neutralising antibody in all immunised people, and that some measure of the likely field effectiveness of a vaccine can be obtained by serological surveys of immunised populations.

TABLE I—NUMBER OF CHILDREN BLED IN EACH YEARLY AGE-GROUP

Age	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
No. of children	13	21	20	17	20	15	17	31	27	19	19	7	15	13	16

TABLE II—WHY BLOOD-SAMPLES WERE NOT OBTAINED

Reason	No. of children	Reason	No. of children
Left the county	40	Away on holiday	1
Not immunised	14	Ill	2
Parents refused to cooperate	10	Dead	2
Child refused to be bled when at clinic	2	Working; unable to attend	2
Venepuncture unsuccessful	2	Consented to attend but defaulted	2
		Not traced	2

Co. Down has a population of about 250,000, half of which is urban and half rural. Since 1946 the incidence of poliomyelitis has been of the same order as that in the United Kingdom generally, but the disease has been mainly in young children because most older children and adults have acquired immunity naturally (Dane, Dick, Connolly, and Briggs 1956). In the autumn of 1957 a large-scale immunisation programme was started using British, United States, and Canadian inactivated vaccine. The vaccine was widely accepted; and by the summer of 1960, when the survey was made, it was estimated that 95% of children over the age of one year had completed, or were completing, a course of three injections.

Materials and Methods

Virus-neutralisation test.—Equal quantities of virus suspension and diluted sera were mixed together, incubated at 37°C for six hours, left at +4°C overnight, and then inoculated into stationary Kahn tubes (3 in. × $^1/_2$ in. diameter) containing monolayer cultures of second-passage monkey-kidney cells. Two tubes were used for testing each virus-serum mixture; and the presence or absence of viral cytopathic effect on the sixth day was recorded. 50 T.C.D.$_{50}$ of Brunhilde type I, Y-SK type II, or Leon type III was used in each test. 0·5 ml. of virus-serum mixture was added to the tubes which already contained 0·75 ml. of medium (Earle's salt solution with 0·5% lactalbumin hydrolysate and 2% inhibitor-free calf serum).

The population sample.—The names of children born on June 1 and Dec. 1 were obtained from the Co. Down child-health register. Parents were asked to bring these children to clinics on specified days so that a blood-sample might be taken. The purpose and nature of the survey was explained, and an undertaking was given that any child found to be in need of a fourth dose of vaccine would be offered this immediately. 5 to 10 ml. of blood was taken from arm veins, and the sera were inactivated at 56°C for thirty minutes, and then stored at −25°C.

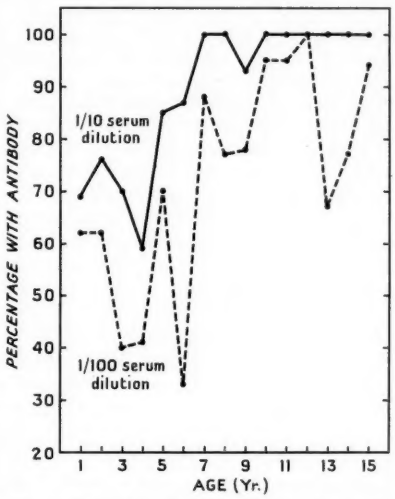

Fig. 1—The percentage of children in yearly age-groups with type-I poliovirus-neutralising antibody.

Results

The response by parents and their children was most satisfactory. Out of a total of 371 children listed, between one and fifteen years old, born on the days selected, blood-samples were obtained from 270 (73%), during April, May, and June, 1960.

The numbers of children bled in each yearly age-group are shown in table I.

The reasons why we failed to obtain a blood-sample were recorded for 79 children out of 101 (table II). In the remaining 22 children the reasons were probably similar. From the data it therefore seems likely that blood-samples were obtained from about 90% of the possible attenders. The largest group of children who might have attended, but did not, were those whose parents had declined to have them immunised.

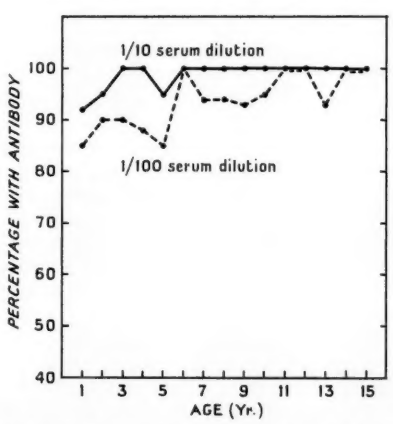

Fig. 2—The percentage of children in yearly age-groups with type-II poliovirus-neutralising antibody.

The results of the tests for neutral-

ising antibody to the three poliovirus types are set out for each yearly age-group (figs. 1, 2, and 3) and diagrammatically for five-year age-groups (fig. 4). 260 children had received three doses of vaccine, and 10 two doses. All 10 children who had received only two doses had antibody to type-II virus, but only 3 had type-I antibody, and 6 type-III.

Batches of vaccine from manufacturers in the United Kingdom and North America had been used in Co. Down, but failure to develop antibody was not found to be associated with any particular make of vaccine.

The relation between the presence or absence of antibody to type-I poliovirus (at a 1/10 serum dilution) and the interval between the time when the third dose of vaccine was given and when the blood-sample was taken is shown for the one-to-five-year age-group in fig. 5. 31 (94%) of 33 children bled within a year of the third dose had antibody levels of 1/10 or greater, but only 30 (64%) of 47 bled more than a year after having the third dose had similar titres ($0{\cdot}01 > P > 0{\cdot}001$). In a few children the intervals between vaccinations were greater than those usually recommended—namely, three to eight weeks between the first and second dose, and six to fifteen months between the second and third. The results for these children did not differ significantly from those for children of the same age vaccinated at the recommended intervals.

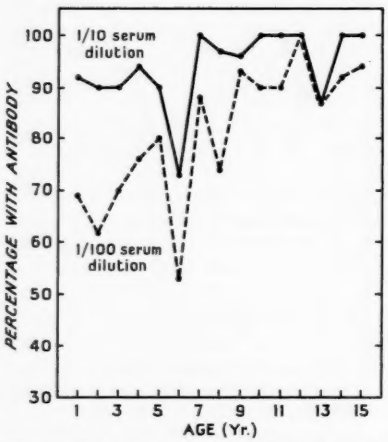

Fig. 3—The percentage of children in yearly age-groups with type-III poliovirus-neutralising antibody.

The blood of all 270 children tested was found to contain antibody to at least one type of poliovirus; and only 8 children had antibody to one type alone.

It is too early to reach conclusions on the effect of poliomyelitis immunisation on the incidence of the disease in Co. Down, but the numbers of paralytic cases since 1950 are of interest (table III).

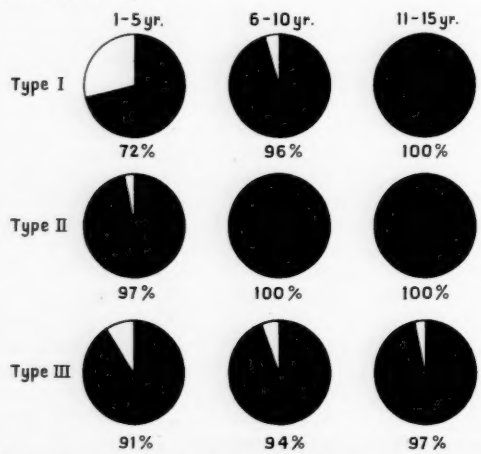

Fig. 4—The percentage of children in five-year age-groups with poliovirus-neutralising antibody at a 1/10 serum-dilution.

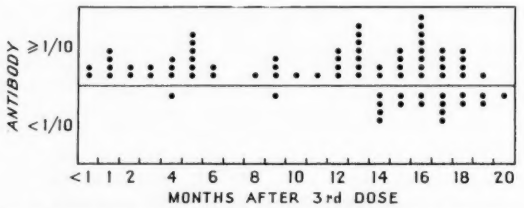

Fig. 5—The presence or absence of type-I antibody in 80 triple-vaccinated children aged 1-5 years related to the time since the 3rd dose of vaccine.

2 of the 1960 cases have been excluded: a man infected in Eire who was admitted paralysed to the Northern Ireland Fever Hospital; and a child, infected in England, who became paralysed the day after arriving in Co. Down on holiday.

Discussion

An obvious difficulty in serological surveys based on random sampling is to obtain enough response. In this Co. Down survey we estimate that about 90% of those who should have been bled were in fact bled. The efforts and enthusiasm of the medical officers of health and health visitors which resulted in 95% of the county's children being vaccinated were also responsible for the high acceptance-rate in the survey.

The tests for neutralising antibody to the three poliovirus types showed a high rate of immunity in the child population. That more of the older children had antibodies than the younger can be explained partly by the larger number who would have naturally acquired immunity to a poliovirus type or types, and partly by the better antibody response to all three poliovirus antigens that can be expected in those already immune to one or two of the viruses. The largest number of non-immunes were found in the one-to-five-year age-group where the influence of previous natural infections would be least. In this age-group the results for type-I (72% with antibody) were significantly lower ($0{\cdot}001 > P > 0{\cdot}0001$), and for type III (91% with antibody) rather less good than for type II. The different responses to the three poliovirus antigens accords with what is known about the relative potency and effectiveness of the three components in the vaccines. The need for protection against type-I poliovirus is obvious. Since 1955, 406 polioviruses have been isolated from cases of acute poliomyelitis in Northern Ireland, of which 91·6% have been type-I, 0·8% type-II, and 7·6% type-III.

TABLE III—COUNTY DOWN: PARALYTIC POLIOMYELITIS, 1950–60

Year	1950	1951	1952	1953	1954	1955	1956	1957	1958	1959	1960
No. of cases	51	9	10	27	9	2	3	27	5	0	2

The relation between the presence or absence of type-I antibody and the time elapsing since the third dose (fig. 5) suggests that nearly all children develop antibody to type-I virus after the third dose, but in a significant number this antibody falls below the 1/10 level in the second year.

That only 3 of 270 children tested should have no antibody to type-II poliovirus (at a 1/10 serum-dilution) suggests that, if the potency of type-I, and, to a lesser extent, type-III antigenic components of the vaccine were increased, almost complete sero-immunity of the population to all three poliovirus types could be achieved. Meanwhile, a fourth dose of vaccine appears desirable in Co. Down to boost the immunity of the younger children to type-I poliovirus. In the past most cases of poliomyelitis

have been in young children, and it therefore seems wise to administer the fourth dose about one year after the third to give maximum protection at the time of maximum risk. Also a better booster effect might be achieved by giving the dose at a time when most children still have detectable levels of type-I antibody (Medical Research Council 1959).

Most children born in Co. Down since 1957 have received their first dose of vaccine between the ages of six and twelve months. In Northern Ireland the incidence of poliomyelitis in infants below the age of one year has been extremely low in recent years. Thus, in the 1957 Belfast epidemic (Donaldson and Dane 1960), only 2·5% of cases were infants between six and twelve months old and there were none under six months.

Protection from passively acquired maternal antibody would account for this relative absence of poliomyelitis early in life. It is known (Perkins, Yetts, and Gaisford 1958) that infants with maternal antibody still detectable respond less well to inactivated poliomyelitis vaccines than those with no passive immunity; it therefore seems logical to continue the present policy of starting to immunise in the second half of the first year of life, when maternal antibody has, in most infants, waned to low or undetectable levels.

Few areas have immunised such a large proportion of their children as Co. Down, and it will be very interesting to see whether the ability of polioviruses to spread through such a community has been impeded. Even if it has, isolated cases or small outbreaks of poliomyelitis might still follow the introduction of viruses from elsewhere. We think that, in such situations medical officers of health should take measures similar to those for combating outbreaks of diphtheria.

Summary

In County Down in 1960 a poliovirus-antibody survey was undertaken among 270 children under sixteen years of age. An estimated 95% of them had received three doses of vaccine.

Immunity to type-II and type-III virus appeared to be satisfactory: 99% had antibody to type-II virus, and 94% to type-III. In younger children the proportion immune to type-I virus was significantly lower; only 72% in the one-to-five-year age-group had circulating antibody, compared with 98% of older children.

In the one-to-five-year age-group 94% tested within a year of receiving the third dose of vaccine had antibody to type-I virus, compared with 64% of children tested more than one year after the third dose.

For younger children a fourth dose of vaccine seems desirable. It should be given about one year after the third, to boost their immunity to type-I virus.

This study was carried out jointly by the university department of microbiology and the Co. Down health department. We wish to thank Dr. J. B. McKinney, the county medical officer of health, and his staff for their enthusiastic cooperation, Dr. E. Cheeseman and his colleagues for statistical advice, and members of the department of microbiology for helping us take blood-samples.

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Personal Papers

REFLECTIONS ON THE NATURE OF SPASM

PETER MCEWAN
M.A., M.B. Edin., F.R.C.S.E.

THE causation of spasm is imperfectly understood. Because it may occur in any part of the human body, its manifestations are very varied, intricate and difficult to interpret. I offer these reflections as those of a doctor who has suffered from spasm for many years.

In the past eighteen months three papers have appeared, from different clinics,[1–3] describing the effects of a new method of treatment upon a group of patients who not only had spastic paralysis of the lower limbs due to spinal disease but also had painful intermittent spasms. The treatment consisted in the intrathecal injection of phenol in lipid solution, originally suggested by Maher in 1955.[4] This acted by a selective destruction of the anterior spinal nerves, and was remarkably successful. A very curious observation was made by all these observers—namely, that in a considerable proportion of cases, after the spasm was abolished, a certain degree of voluntary power over the limbs was regained, the existence of which had not previously been known or suspected. It was clear that so long as the nervous currents producing the spasm were active, they inhibited or masked certain other nervous currents.

Last year Nathan,[5] one of the above writers, demonstrated a similar phenomenon in a quite different group of patients, who had a lesion in the central or peripheral nervous system causing pain or local tenderness. When these symptoms were cured, by methods similar to the above, Nathan found that the perception of certain stimuli (touches or the discreteness of pinpicks) was improved, and the improvement was evident even when a large number of peripheral nerves supplying the part had been destroyed. In other words, the pathological nervous impulses could inhibit or impair the normal sensory impulses.

Eysenck [6] describes "a general law discovered by Pavlov and called by him Negative Induction; by which Pavlov meant the experimental demonstrable fact that a positive stimulus applied in one part of the brain may cause the depression of activity in other parts of the brain". The same principle holds in the everyday working of the human brain, whether emotionally or intellectually. Terror may hold a man rooted to the spot. Deep emotion may render him speechless. Concentration on study, or even on an interesting book, or rapt attention to music, may render him unaware of what is happening around him.

It appears, therefore, that in the working of the nervous system, whether physiologically, or experimentally, or in pathological states either motor or sensory, there is a general law—that currents flowing in one channel of the nervous system are able to inhibit, more or less completely, the flow of nervous impulses along one or more of the other channels.

PERSONAL OBSERVATIONS

Before considering the possible application of this law, let me briefly describe my own spastic movements, which I believe are typical, being those of a spastic paresis of

1. Nathan, P. W. *Lancet*, 1959, ii, 1099.
2. Kelly, R. E., Gautier-Smith, P. C. *ibid.* p. 1102.
3. Leversedge, L. A., Maher, R. M. *Brit. med. J.* 1960, ii, 31.
4. Maher, R. M. *Lancet*, 1955, i, 18.
5. Nathan, P. W. *J. Neurol. Neurosurg. Psychiat.* 1960, **23**, 202.
6. Eysenck, H. J. Sense and Nonsense in Psychology. Penguin Books, Harmondsworth, 1960.

both lower limbs, about equally. I can stand on the lawn, unsupported, erect and natural, provided I keep almost imperceptibly on the move and provided I devote part of my attention to keeping my balance: if I use a stick or take hold of a support, my attention is set free. If I try to walk, the spasm sways me so that I find it hard to keep my balance. I no longer try, being almost certain to fall. When I use my stick I can walk well—but my trouble is bending upwards of my thigh so as to make my feet clear the ground. Despite my utmost effort this movement is slow, weak, and very incomplete, flexing the thigh only to 30 or 40°. My walking speed is a maximum of 1 mile an hour, my range about a mile. Going up steps, I must use a rail. Going downhill, I use short steps, and keep my knees fairly stiff because if I bend them quickly or far, I would lose control and collapse; a typically spastic gait.

The explanation of this gait seems clear enough. When I recovered from my complete paralysis, the recovery of voluntary control of the movements of my lower limbs was incomplete. It stopped short. So my movements are still weak and limited. The lower motor neurone therefore loses part of its control from above and the reflexes are exaggerated: my legs are spastic.

That the above is the generally accepted explanation is clear from the answer given by an expert to the question " What is the cause of spasm in cases of spastic paralysis ? " in the *British Medical Journal* [7]:

" The increased muscle tone in spastic paraparesis is due to inhibitory impulses from the brain stem and higher centres being interrupted, with resulting increased activity of spinal reflexes. The flexor spasms which may occur are part of a mass reflex, and they may be precipitated by anything touching the legs."

I have never been satisfied with the above explanation. As I lie in bed and contract the muscles of my thigh, they feel hard and fairly strong, and I feel I could walk normally. As soon as I try to do so, the spasm comes into action. My theory is this. When the normal person wishes to bend his thigh the message sent from his brain consists of two sets of impulses, one a positive set causing the contraction of certain muscles, the other a negative set causing the relaxation of the antagonistic group: so perfectly coordinated as to cause rapid and graceful movement. In the spastic, these messages when they reach the spinal lesion become disordered. Part of the positive message passes to its correct destination. The negative is inhibited, in accord with the law of inhibition stated above. Further, part of the positive message is transferred to the antagonistic muscles. Hence the resultant movement is slow, weak, incomplete. If enough of the positive message is transferred to the wrong channel, the person can no longer walk.

Denny-Brown's Croonian lectures for 1960 contain the following passage:

" Coinnervation of antagonists during attempted voluntary movement in athetosis and chorea was thought by Wilson (1925) to represent the primary disorder of motor function in these states. Our investigation indicates that each such spasm is an exaggeration and conflict of the normal reflex factors essential for all movement." [8]

Let me now try to apply the above principles to my own case. My disability is diagnosed as " spastic paraparesis ". I am of the opinion that this is a misnomer. I believe that I no longer suffer from paresis, but only from spasm. I believe that if the spasm were eliminated, I could at once walk and run like a normal person. My muscles are of normal power, but this power is masked by the spasm. I could give many clinical reasons for this opinion, but merely wish to put it forward. I think it is generally true of cases like my own. If it is also true for cases so severe as to be incapable of voluntary movement: it raises the question whether the term " spastic paralysis " is logical and is not a contradiction in terms.

What I would like to know is the factors which make the spasm better or worse. I found that when I was uræmic, the spasm became much worse, and recovered rapidly when the uræmia abated. Beyond that, I do not know the exciting causes. I have the faint hope that a spasm-controlling drug may be found.

THE PROBLEMS

The unsolved problems seem to me to fall chiefly under five headings.

1. The measurement of spasticity. Kelly and Gautier-Smith express it thus: " So far, no objective means of measuring spasticity have been found and clinical observation remains the best method. Range of movement measurements are inaccurate and electromyograph records show much daily variation. The degree of spasticity frequently alters from day to day and, as Kuhn and Bickers (1948) pointed out, suggestibility plays a very important part in invalidating results."
2. The measurement of power. Seeing that voluntary movement is inhibited while the spasm is present, the power cannot be assessed by present methods.
3. The development of a maximum motor response to a minimal sensory stimulus.
4. The presence or absence of pain in cases that seem otherwise exactly similar.
5. The mechanism at the site of the spinal lesion which is causing the spasm.

All these problems present a challenge to research.

7. *British Medical Journal*, 1959, ii, 1197.
8. Denny-Brown, D. *Lancet*, 1960, ii, 1155.

Special Articles

UNRESTRICTED VISITING IN A MENTAL HOSPITAL

An Inquiry into its Effects and Nursing-staff Attitudes

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RESTRICTIONS on the visiting of patients in hospital is general and traditional, though exceptions are usually made for the seriously ill. Reasons for restrictions are not easily discerned. Infection, a risk attending most human intercourse, applies to only a few patients; other reasons may be specious and, therefore, suspect. Valid reasons may exist, but they appear to be exceptional and seldom last for long.

That restricted visiting to patients in mental hospitals could be detrimental by decreasing contact with the outside world was a view held by one of us,[1] and in February, 1960, daily visiting at any time from 9 A.M. to 9 P.M. was encouraged at Severalls Hospital. The effect on visiting was not dramatic, but there seemed to be notable changes in the attitudes of nurses. After six months, a

1. Barton, R. Institutional Neurosis. Bristol, 1959.

TABLE I—DIFFICULTIES EXPECTED AND THOSE ACTUALLY ARISING FROM UNRESTRICTED VISITING

Difficulty	West Park expected (55 replies)	Severalls (52 replies)	
		Expected	Occurring
Interfere with ward routine	87%	67%	35%
Be bad for patients	43%	2%	0%
Relatives would not work	11%	6%	2%
Interfere with treatment	83%	40%	13%
Make other patients dissatisfied	47%	12%	2%
Embarrass the staff	26%	10%	8%
Take up too much nurses' time	57%	25%	6%
Others	26%	8%	6%

There is a similarity in the rank order of the difficulties anticipated by the nursing staff at West Park Hospital and at Severalls ($\rho = 0{\cdot}85$; significant at the 0·01 level).

questionnaire was sent to every sister and charge-nurse asking (1) whether initially they had been in favour of unrestricted visiting; (2) whether the expected disadvantages had in fact arisen; and (3) what the general effect had been.

At West Park Hospital, used as a control hospital, where a liberal policy had been pursued but visiting had not become officially unrestricted, a questionnaire covering the same points was circulated to all sisters and charge-nurses.

The Responses of the Staff

In each hospital the questionnaires were to be completed anonymously and returned to Dr. Elkes in sealed envelopes. The usual administrative channels of communication were avoided.

52 of the 58 sisters and charge-nurses at Severalls replied, and 55 of the 60 sisters and charge-nurses at the control hospital —90% and 92% respectively.

It is interesting to compare the main difficulties expected at West Park Hospital with those foreseen by the nursing staff at Severalls; and also to note the actual occurrence (table I).

Probably the generally lower incidence of expected difficulties at Severalls was a function of retrospective judgment rather than of any fundamental difference in attitude between the two staffs.

At Severalls, 52% reported that no difficulties had arisen. Of the 42% who reported difficulties, the greater part (90% of this subgroup) found them seldom and rated them as " trivial ". 6% of the group did not answer the question.

Both groups were asked to suggest an ideal number of hours and days per week for visiting and to say whether written permission should be necessary. Considerable differences were found between the two hospitals (table II).

We tried to evaluate the general effect of the change at Severalls. The opinions of the nurses were predominantly favourable. Although some additional demands had been made on the time of the nurses, 86% of the group thought this time was well spent. 75% stated that no inconvenience had been caused to the nurses or to the routine of the hospital. Unrestricted visiting was felt to benefit the relatives by 83% of the group, and the patients by 52%.

TABLE II—SUGGESTED IDEAL VISITING TIMES AND ATTITUDE TO WRITTEN PERMISSION

Recommendation	West Park (55 replies)	Severalls (52 replies)
Visiting days per week		
Less than 4	40%	2%
7	42%	86%
Hours per week		
0–10	54%	2%
11–30	16%	10%
31–60	12%	25%
61–84	2%	55%
Not answered	16%	8%
Should written permission be necessary? YES	46%	10%
NO	54%	81%

In no instance was a generally adverse effect reported in either relatives or patients, although isolated instances of temporary disturbance were mentioned by 6% of the group.

Effects of the Change

The effects produced at Severalls Hospital together with previous experience of unrestricted visiting in certain wards in another psychiatric hospital (Shenley) prompts one of us (R. B.) to discuss his impressions and opinions—for what they are worth.

No spectacular changes result from removing restrictions on visiting. The number of visits gradually increases, because the removal of restrictions probably enables relations to fit in their visits with their work and other obligations more conveniently. Sometimes, a dedicated relative may need advising to look to her own health if she seems to be tiring herself out by too frequent journeys, but staff should examine their motives before giving such advice.

There are insidious effects. Visiting regulations can no longer be quoted to support unnecessary authority; the privilege of visiting at hours other than those stipulated by hospital authorities cannot be used (unconsciously or otherwise) to make visitors feel under an obligation to the official staff, nor can it be withdrawn lightly at the whim of those in charge.

The reputation of the hospital benefits greatly, not only because it appears less restricted and bureaucratic but also because relations can visit patients and wards at any time, and suspicions that " everything is prepared " for visiting hours can be countered. Encouraging visitors to be present at any time also gives them a chance to acquire a first-hand knowledge which can counteract sensational suggestions in the Press that patients are ill-treated. Unrestricted visiting gives them an opportunity of seeing the enormous amount of kindness and good work that is, and always has been done, in mental hospitals.

The direct effect on patients is hard to assess. Simultaneous changes in the hospital may have been responsible for the improvements. The patient benefits directly from his awareness that hospital policy keeps restrictions to a minimum and visiting is possible at any time; and there is probably also an indirect benefit from the subtle changes of staff attitude resulting from an officially recognised liberal policy.

A therapeutic situation may arise when the end of a relative's visit is determined by the relationship between patient and visitor and not by the hospital. The ward doctor or the sister, by gently and repeatedly pointing out to the patient that their demands on their visitors' time have been unreasonable may, if this is skilfully done, help the patient to useful self-criticism and possibly to a more reasonable approach to others.

Visitors are asked to notify patients when they are coming either by telling them, or by letter or postcard. If such private arrangements have not been made, visitors are warned that patients may not be waiting for them. Again if patients are working during the day, visitors are told that work is a part of treatment and they are asked to cooperate where they can by not interrupting the patient's work. Encouraging visitors and patients to make their own arrangements in this way whenever possible, makes the relation realise that authorities consider their patient a responsible person and makes the patient less dependent for decisions on routine and authorities, thus fostering the independence that is vital if the patient is to live in the community.

Summary

A questionnaire was sent to all sisters and charge-nurses at Severalls Hospital to find out their attitude to unrestricted visiting, the difficulties anticipated and actually encountered, and their reactions after six months' experience of the system. At a control hospital (West Park) where visiting is not officially unrestricted a similar questionnaire was circulated.

The results indicated that unrestricted visiting had not produced the difficulties expected, either in frequency or degree. Both patients and relatives were said to have benefited, and disadvantages were trivial.

During the six months' experience of unlimited visiting at Severalls Hospital the attitude of the nurses changed in favour of the new system.

We record our thanks for the assistance and cooperation given by Dr. Theodore Schlicht, the medical superintendent of West Park Hospital, and the sisters and charge-nurses of West Park and Severalls Hospitals.

GENERAL MEDICAL COUNCIL

IN his address at the opening of the Council's 202nd session on May 30, Sir DAVID CAMPBELL, the president, said that a report by a special committee reviewed changes in the curriculum made or suggested in individual schools. These included the introduction of courses in special aspects of the basic sciences; the abolition of the written and practical portions of the second M.B. examination, which would be replaced by a faculty assessment of the candidate's record, supplemented by an oral examination; an interchange of teachers in the preclinical and clinical subjects, and the institution of combined lectures and demonstrations; an increase in the time spent in residence in hospital in the various clinical departments; and the introduction during the clinical period of elective courses and some " free time " before the final examination.

The increase in the number of Commonwealth qualifications recognised for the purpose of full registration was matched by the annual increase in the number of Commonwealth practitioners actually granted full registration. Table C of the Medical Register showed that in 1960 no fewer than 1296 Commonwealth practitioners were granted full registration—over a third of the total of 3473 practitioners granted full registration in that year. There were corresponding increases in the number of Commonwealth practitioners granted provisional registration, and in the number of Commonwealth and foreign practitioners temporarily registered.

The impending withdrawal of the Union of South Africa from the Commonwealth was of special concern to the Council because of its reciprocal arrangements for registration and the cordial relations which it had long enjoyed with the South African Medical and Dental Council.

"We shall all hope—and I think I may say we confidently expect—that the changed political status of South Africa will not affect the reciprocal arrangements for registration which have existed between this country and South Africa since 1921. A Bill now before Parliament will enable these arrangements to continue as at present for a period not exceeding twelve months, which will allow time to consider any adjustments in detail that may need to be made."

In England Now

A Running Commentary by Peripatetic Correspondents

Greek, we all know, is a dead language—mutton-dead. No right-minded aspirant to medicine wastes precious brain-space learning even its alphabet (queer word, that; seems un-English somehow; probably Arabic). And even if he did, one of our ancient universities would whip him into line again quick enough, poor boob.

Dead it is, and quite right too. Yet in the vocabulary of late 20th-century medical science time and again it rears its hydra-head and no-one flattens it with a sexton's spade or bids it lie down like a good cadaver. Isn't it time we ended this unseemly anomaly (still another queer word), took away the English-Greek lexicon from the back-room boy who makes the words, handed him *Liddell and Scott*, and bade him do the jargon into English p.d.q.? What age and country does he think we are living in?

We could start with path. reports. Thus: " The red little bodies varied in size and shape and took up many stains. The buffy coat settled 10/1000s in one hour." All quite refreshing, but when you reach the white cells it's more difficult, and it may be that our back-room boy, talented though he clearly is, might have to confess that his tricks are irreversible and that he, like the rest of us, has quite lost the power of Adam and the Folk to make new words for new things seen.

If the poor chap really is beaten, might not the aspirant do well, after all, to learn his alpha-beta, so that he could at least look up ποικίλος, φιλέω, and χρῶμα and perhaps even defeat the examiners by his unexampled skill in telling tops from trops and both from trophs.

* * *

I am seated with my fellow guests at the bar. We have reached the stage of guessing each other's occupations. After the second whisky I am asked: " What business are you in? " " I'm not really in business at all." " Profession? " " Hmm." " Doctor, I expect." " Yes, I'm afraid so." " G.P. I suppose. You people are doing all right these days—pay awards and so on." " Hmm." " Where do you practise? " " Well actually I'm a specialist." " Oh, you'll be a surgeon? " " No." " A medical specialist then? " " N-no." " What *do* you do? " " I'm a psychiatrist actually."

This announcement is followed by a slight hush during which one can hear the mental screw being tightened, the bolts shot home, and a rapid reintegration of personalities taking place. Thereafter, heavy drinking is done more surreptitiously and parents fear to strike their brats in my presence. People accuse me of sizing them up, ask whether I do not find my work depressing, and insist on giving me the details of old Uncle George's senile dementia.

I am not sure that it is not easier for the general practitioner. He only has to interrupt his sunbathing to prescribe for sprained ankles, bee-stings, and sunstroke.

* * *

My peripatetic colleague who was impressed by American ingenuity in disposal of razor blades might be interested to know that during the late war when scrap iron and steel were desperately needed, enterprising people in some hotels remembered these deposits and several large troves of valuable metal were salvaged. I believe more than a ton was rescued from one cache. Thus the " ingenious " Americans put their earlier careless waste to some good.

* * *

News from School.—In the afternoon we went for a bike ride, and went for a picnic. I was surprised how well I got on, because a bicycle is rather a new form of transport for me, but I have been practising and going for short rides for about a month now. I find it still very exhausting up hills, even if the slope is almost invisible my legs are not muscley enough! But down hill is really great fun I think, and not so heating, because the wind is in your face and cools you. It was really great fun, but it will never take the place of a pony. For one thing a bicycle is not a companion, it may be faster on the roads, and much cheaper to keep up, but even so . . .

Letters to the Editor

MEDICAL EMIGRATION

SIR,—In his interesting article of May 20, Dr. Davison uses figures on medical emigration to Canada to suggest that evidence presented to both the Willink committee and the Pilkington commission grossly underestimated the loss of doctors from the United Kingdom. A recent investigation of my own designed to elicit somewhat different data supports his view, and incidentally suggests that the figures he obtained from our Department of Citizenship and Immigration also underestimate the flow of British doctors to this country.

The registrars of our ten provincial medical licensing authorities provided me with the number of new registrants for the years in question, divided into registrants who are graduates of Canadian medical schools and registrants whose qualifications were obtained elsewhere. The gross figures are:

	1955	*1956*	*1957*	*1958*	*1959*	*Totals*
Canadian	954	909	891	819	811	4384
Non-Canadian	447	496	582	557	586	2668
	(195)*	(214)	(311)	(202)	(182)	(1104)

*Citizenship and immigration figures on immigrant British doctors.

Any compilation of new registrants by provinces involves a degree of duplication since a doctor may register in one province and subsequently move to another. Two separate registrations would then be reported and the figures for non-Canadians are consequently high. We have, for our purposes, compensated for this by recording the total number of registered, active resident physicians by provinces at year end. The extreme example of professional mobility is provided by Newfoundland which had 199 fully registered physicians at the end of 1954 and 275 at the end of 1959, but in the intervening five years had registered 456 new non-Canadian doctors.

The other reservation is that my figures indicate new registrants by provinces from all non-Canadian sources. I am aware of the fallacy of attempting to compare oranges and bananas but it is a fact that the overwhelming majority of our medical immigrants come from the United Kingdom and Eire. The figures quoted will therefore represent relatively few new registrants from the rest of the world.

Six of our provinces have a reciprocal arrangement with the General Medical Council, whereby registered medical practitioners on the "Home List" may register without further examination. Not unnaturally, medical immigration from the U.K. is heaviest to those provinces and in several of them the registration of non-Canadian doctors actually exceeded the registration of natives during the years under consideration. The racial characteristic of the medical population of this country is undergoing a change and there are some who view this with apprehension—as reflected in the remarks quoted by Dr. Davison.

Such facts as I have been able to assemble and interpret, as well as my own impressions, all serve to confirm that the tide of medical emigration has been flowing strongly from Great Britain. We in Canada have gained an increment in medical manpower which has permitted us to maintain or slightly improve our physician/population ratio despite a rapid increase in the general population. We are aware that we should not depend on this favourable circumstance and we are taking steps to become self-supporting for our future medical needs.

Toronto, Ontario. A. D. KELLY
General Secretary, Canadian Medical Association.

SIR,—Dr. Davison's conclusion (May 20, p. 1107) that money is necessary "for discovering why so many doctors prefer to practise abroad" is surely rather fantastic?

I could suggest several reasons, but one thing that must not be forgotten is that long before 1948, for centuries almost, there were always many for whom the life and work of a consultant or G.P. in this country had no appeal: who wanted something more highly coloured, and were prepared to risk quite a lot to get it. Many, too, to whom it seemed a duty to go where they were most wanted. I hope there still are. Who in this over-doctored country can feel that he is really needed? It may be one kind of satisfaction to beat dozens of competitors to a post or a practice: but it is another, and better, to be filling a gap which but for you would remain unfilled.

For such, the Indian Medical Service and the various colonial services catered pretty well. Now these outlets are closed, obviously they must seek elsewhere.

We may justly resent the attitude long prevailing in home medical circles that going abroad to practise is either a confession of failure or there remain obscure reasons for it.

Bristol. GEORGE L. ALEXANDER
Colonial Medical Service (retd.).

THE FIBERSCOPE

SIR,—I was interested to read Dr. Hirschowitz's account of his experience with the fiberscope (May 20), and, in particular, his findings with regard to the duodenal bulb and its distal sphincter.

Forty-five years ago, in 1915, Keith [1] first described the three well-known sphincters in the alimentary tract; and in the same year Alvarez [2] added descriptions of four more, including one in the duodenal wall just proximal to the ampulla of Vater. Both Keith and Alvarez based their findings on histological evidence of significantly increased concentrations of the myenteric plexus (so-called "pacemakers") at the sites of the sphincters. Keith also demonstrated the autonomic supply of the bulb from the cœliac plexus, while in 1953 Mitchell [3] showed that two branches of the anterior vagal trunk supplied the bulb as far as its apex. In 1956 Milton and Smith [4] demonstrated that the duodenal pacemaker in dogs was in the vicinity of the ampulla of Vater, and in 1942 Torgerson [5] had shown, in dog, horse, and man, how the circular muscle coat at the distal end of the bulb is considerably more powerful than in other regions of the bulb. In 1953 Janker,[6] working in Bonn with cine-radiography, clearly demonstrated filling and emptying of the bulb and showed that under normal conditions when the pylorus is open the bulb sphincter is tightly closed. Embryologically it is still controversial whether this sphincter (the bulb sphincter) does or does not mark the junction between the the foregut and midgut.

After nearly half a century all these facts have now been confirmed by direct observation by Dr. Hirschowitz and his colleagues.

Some three and a half years ago I showed an experimental series of pictures of a barium meal on myself to Prof. C. A. Wells and Dr. P. H. Whitaker of Liverpool, in which a bulb sphincter at the apex of the first part of the duodenum could be clearly seen.

In the past four years I have performed duodenotomy on every case of duodenal ulcer treated surgically and demonstrated in almost every one a definite thickening of the muscle at the distal end of the first part of the duodenum. It is possible that agenesis of this sphincter in a small minority of cases may account for the post-bulbar ulceration described by Cooke and Hutton [7] and Portis and Jaffe.[8] In addition I have been able to show conclusively that the bulb is, in the vast majority of cases, empty of bile, and is only filled from below after digital dilatation of the bulb sphincter.

Partly on the above and partly on other theoretical considerations, I have, in the past four years, practised a surgical procedure for duodenal ulcer which avoids completely any form of

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8. Portis, S. A., Jaffe, R. H. *J. Amer. med. Ass.* 1938, **110**, 6.

gastrectomy with its possible complications and morbidity. It is equally applicable to uncomplicated ulcer in any site of the bulb, or ulcer complicated by stenosis or massive hæmorrhage. The first five years' experience of this method will be reported in due course.

I am sure that the fiberscope represents a tremendous step forward in diagnosis, running radiography a very close second, and may eventually supplant it.

Peterborough, Northants. D. W. BRACEY.

FŒTAL HÆMOGLOBIN SYNTHESIS IN SOME HÆMOGLOBINOPATHIES

SIR,—Using the acid hydrolysis method for the detection of red cells containing fœtal hæmoglobin, Dr. Mitchener and his colleagues (May 27) reached the conclusion that in sickle-cell anæmia the Hb F, which accounted for 8% of the total hæmoglobin in the case quoted, was contained in cells that are distinct from those (the majority) that contain Hb S. From this they argue that separate clones of erythropoietic cells coexist, each manufacturing a distinct hæmoglobin type. On this and certain other points our results, shortly to be published,[1] are in disagreement.

Briefly, we find that cells containing Hb A, and the variants C, D, G, and J, are hydrolysed in a buffer at pH 3·4. The hæmoglobin of fœtal cells is insoluble, but just before, and for some weeks after birth, red cells appear from which only part of the hæmoglobin is removed by acid hydrolysis, and from the 16th to the 30th week of life, when adult cells have appeared and wholly fœtal cells have completely disappeared, these "intermediate" cells are still present. Since at this time appreciable amounts of Hb F are to be found in a hæmolysate, we conclude that at this period Hb A and Hb F are both incorporated in the same "intermediate" cell.

In thalassæmia major, where Hb F production is high, all the cells fail to hydrolyse. In thalassæmia minor, all the cells show partial hydrolysis, retaining a proportion of hæmoglobin that is greater than can be accounted for by the low proportion of Hb F (up to 3·5%) present in our cases. It would appear therefore that some of the hæmoglobin in thalassæmia minor, though identical with Hb A by other criteria, is in fact a molecular variant, as postulated by Ingram and Stretton.[2]

We found also that in sickle-cell anæmia (Hb F 8–17%), no hæmoglobin was extracted by hydrolysis from any of the cells, Hb S behaving in this respect as Hb F. This is a different result from that found by Mitchener et al., and we have not seen the appearances illustrated by these authors in their figure B except in a child with thalassæmia major, who we subsequently learned had been receiving regular transfusions of adult blood. In Hb S/C disease about half the hæmoglobin was eluted from all the cells, as expected; but in sickle-cell trait (Hb A/S) a much greater than expected proportion was retained. In the Hb E trait, also, there was partial retention of hæmoglobin. It is of interest that Allison [3] has remarked that the Hb types that we found to be insoluble—namely, Hb F, Hb S, Hb E, and the Hb of thalassæmia—are precisely those known or strongly suspected to be resistant to the multiplication of malaria parasites.

In general our results (which will be expanded elsewhere) indicate that both in neonatal and adult life, when Hb F appears in the blood it is incorporated together with other hæmoglobins in one and the same cell; and we see no need to postulate separate clones of erythrocyte precursors each devoted to the synthesis of a single hæmoglobin type.

A. B. RAPER
Bristol Royal Hospital, Bristol. I. D. FRASER.

1. Fraser, I. D., Raper, A. B. *Nature, Lond.* 1961 (in the press).
2. Ingram, V. M., Stretton, A. O. W. *ibid.* 1959, **194**, 1903.
3. Allison, A. C. Personal communication, 1961.

COMPENSATION FOR CUPIDITY?

SIR,—In your leading article of May 20, you ask whether the time has not come for a Government inquiry into compensation neurosis. Is it really necessary, or advisable, to invoke such cumbersome machinery?

Surely the time has come for Industry, subsidised perhaps by the insurance companies, to provide a full accident service, independent of the National Health Service, for industrial accidents. Let the injured workman suffer no loss of earnings; and let him be provided with some light work, compatible with his disability, at the earliest opportunity. The facilities and skill necessary for the treatment of most accidents are in the hands of the orthopædic surgeons. Could not the representatives of Industry approach the British Orthopædic Association on this topic?

Many of us general practitioners, aware of the misery that sloth brings, exert ourselves to nip accident neurosis in the bud. Seemingly, however, many regard their patients as "customers" who are "always right"—to be agreed with and not to be reasoned with.

Barton-on-Humber, Lincs. S. H. F. HOWARD.

PSYCHIATRY FIFTEEN YEARS AHEAD

SIR,—We were interested to read Dr. Jacobs' letter of May 13 and the papers by Dr. Smith and by Dr. Brook and Dr. Stafford-Clark last week.

Dr. Jacobs rightly stresses the urgent need for "much smaller and more human-sized psychiatric units in the communities they serve", and most psychiatrists would agree that a moderate-sized unit of, say, 200–300 beds would have many advantages to offer as compared with the large mental hospital.

It is clear from Dr. Smith's interesting paper that in the 170-bed unit he describes only 51 beds are in use for new admissions and that "this to a lesser degree holds good for many of the other units". The unit that Dr. Jacobs describes presumably also caters for a considerable number of chronic patients.

We find it difficult to justify the retention of medium-stay and long-stay patients in such a unit. Their needs are different and they are best cared for and treated in separate units, where the emphasis is on rehabilitation.

The question of the size of future psychiatric units is a matter that requires careful thought, because otherwise we may reproduce many of the old problems and difficulties by building units that are still too large. As it is the intention of the Minister of Health to have psychiatric units in general hospitals, would it not be appropriate to think in terms of the general-hospital pattern and restrict the size of the unit to what is considered adequate in the medical or surgical unit—i.e., 60–80 beds. This is the figure suggested in the Platt report on medical staffing in the hospital service, as being the basis of the medical firm, which may consist of two consultants, a registrar, and two housemen. However, in view of the relatively greater time that must be spent on the psychiatric case compared with the medical or surgical case, we would favour a unit of no more than 60 beds.

One of us (H. S. C.) has experience of one such unit of 56 beds, where only acute, early, and short-stay patients (4–10 weeks) are treated, both as inpatients and day-patients. The annual admission-rate is in the region of 500 and could be higher if more medical staff were available. Used in this way, a unit of 60 beds is large enough to serve a community of about 300,000.

In addition to day-patient facilities, each unit should also have a small nursery for the very young children of mothers attending for treatment, and full supporting outpatient services. The number of day-patients attending at any time would be approximately half of the number of inpatients.

For the present both medium-stay and long-stay patients should continue to be treated in the existing mental hospitals, and therefore rotation and interchange schemes of medical, nursing, and ancillary staff should, if possible, be operated. The

consultants could divide their time between both types of hospital.

This would allow for evolution to a point where the needs of the very mixed group of chronic patients left over could be assessed and provided for in special units. Integration with the general medical services will in our opinion help recruitment at all levels and would absorb almost all the trained staff we have today, thus obviating the sense of isolation that some fear.

We would urge that experimental psychiatric units of the type suggested be provided in a proportion of the general hospitals of each region as a matter of urgency and that every encouragement be given to the admission of suitable psychiatric patients to general wards, as described in the scheme of Dr. Brook and Dr. Stafford-Clark, both as an interim measure and as a permanent arrangement for the treatment of those patients who require a combination of medical and psychiatric treatment.

Bexley Hospital, Bexley, Kent.

H. S. CAPOORE
D. M. LEIBERMAN.

STANNOSIS

SIR,—I was most interested in the paper on tin-oxide pneumoconiosis by Dr. Robertson, Dr. Rivers, Mr. Nagelschmidt, and Mr. Duncumb (May 20), since I believe that I was the first to diagnose this condition in Liverpool.

The patient was seen in 1946. He had the typical X-ray appearances, but in addition he had a hilar mass; and he died from a carcinoma of the bronchus. The diagnosis of tin-oxide pneumoconiosis was made retrospectively in 1948, after Pendergrass and Pryde published their paper.[1]

Since then, I have seen the X-rays of 2 other patients with tin-oxide pneumoconiosis who died from carcinoma of the bronchus. The incidence of 3 confirmed cases of bronchial carcinoma in association with a comparatively rare condition may be fortuitous; but I think nevertheless that it should be placed on record for future evaluation.

Liverpool, 18

GEORGE ANSELL.

ATHEROMA IN THE BANTU

SIR,—I feel I must reply to Dr. Laurie and Dr. Woods' letter of April 1, primarily because they commented rather scathingly about King Edward VIII Hospital in Durban. This hospital is now the teaching hospital of the Medical School of the University of Natal—and we have advanced a long way since the time Dr. Woods mentions, a time when there was grave staff shortage.

In my article I thought I made it clear that our clinicians, in general, regard angina pectoris as rare in the African. The physician who occupies Dr. Woods' previous post at Edendale Hospital also finds angina uncommon apart from syphilitic aortitis. I cannot accept Dr. Laurie and Dr. Woods' view that clinicians' failure to recognise well-established causes of cardiac failure accounts for the high incidence of cardiomyopathy. Some variations between clinical and necropsy findings are inevitable when one is not dealing with the same group of patients. As for the "curious South African belief that the Bantu are immune to certain diseases", I would point out that I always have taught my students in pathology that the African is subject to the same diseases as other racial groups, but nevertheless the incidence of certain diseases unquestionably differs—for instance, we rarely see acute myocardial infarction.

Knowing what material was examined histologically in Dr. Laurie and Dr. Woods' investigation, I question their statement that "there was such a close correlation between the amounts of myocardial damage and the incidence of ischæmia-producing conditions". At that time the histological work from Dr. Laurie's hospital was undertaken in the central laboratory in the department of pathology in the Medical School. I may have seen an occasional section of myocardium, but I did not report on their material as an independent worker. In discussion with the pathologist who was in charge of the routine division I criticised the use of the term "ischæmic fibrosis" in reports where we had no evidence of vascular disease and I expressed doubt on the value of the investigation since we had no idea (several pieces of tissue in the one container) what part of the myocardium we were examining. I know of no systematic grading of degrees of fibrosis or of its anatomical location.

Myocardial fibrosis is not necessarily due to ischæmia. Nor is atheroma the sole cause of ischæmia. Hypertensive arteriosclerosis produces narrowing of small arteries and hypertension is a common condition in the African. I wonder whether Dr. Laurie and Dr. Woods distinguish between atheroma and arteriosclerosis?

Department of Pathology, Faculty of Medicine, University of Natal, Durban.

J. WAINWRIGHT.

APPROVED NAMES

SIR,—I am struck by the great length of the approved names for drugs.

Your issue of May 13 listed twenty-two drugs with proprietary and approved names. Twenty-one of the official names were longer. None was shorter. One was the same.

Why do the Pharmacopœia Commission choose such long names when the Ministry prefer us to prescribe official preparations rather than their expensive proprietary counterparts?

Do they really expect doctors will trouble to write "viprynium embonate" when the trade name is 'Vanquin' just to save the Ministry from losing money? Not many doctors are so well behaved and so anxious to please the Minister that they will strain both their memories and their pens with these prolix creations of unimaginative officials.

Anyway, I shall not.

Central Middlesex Hospital, London, N.W.10.

RICHARD ASHER.

ARTIFICIAL PNEUMOTHORAX

SIR,—Your obituary notice of Dr. Claude Lillingston (May 6) mentions that he was perhaps the first Englishman to be treated with an artificial pneumothorax, though the method had been suggested by Carson some 60 years before. He may have been the first success; but the method had been suggested in 1756 [1] and carried out by Carson in 1822 and 1823,[2] by Ramadge in 1827,[3] by Cayley and Hulke in 1885,[4] and probably by Douglas Powell in the 1880s.[5]

Again the reasons which caused Holmboe to induce an artificial pneumothorax in Lillingston at Mesnalien in 1909 were not, strictly speaking, due to Forlanini's teaching, but to Brauer, who was responsible for the revival of the method; for Brauer's works were read more widely in the period 1905–09 than any of those of the Italian or American phthisiologists.

Lillingston was most concerned with the history of tuberculosis and thus I hope, Sir, you will not regard this letter as pedantic. I would add that his passing has removed one of the last remaining great names in the mechanical medical treatment of tuberculosis. More than anyone he was responsible for the introduction of artificial pneumothorax into this country; and his water-air displacement machine, which now rests in that quiet Valhalla for surgical triumphs, radically changed the whole outlook of many a consumptive and saved countless others.

Killingbeck Hospital, Leeds.

THOMAS MARMION.

1. Pendergrass, E. P., Pryde, A. W. *J. industr. Hyg.* 1948, **30**, 119.

1. Gilchrist, E. Use of Sea Voyages in Medicine. London, 1756.
2. Carson, J. An Inquiry into the Causes of Respiration; of the Motion of the Blood; Animal Heat; Absorption; and Muscular Motion; with Practical Inferences. London, 1833.
3. Marmion, T. *Acta davos.* 1955, **2**, 14.
4. Marmion, T. *Tubercle*, 1957, **38**, 63.
5. Cayley, W. *Brit. med. J.* 1885, **i**, 991.

ACKNOWLEDGMENT

SIR,—I have followed the correspondence on reprints with interest, and with not a little surprise at the passions it evoked. I feel, however, that a problem of far greater moment is the acknowledgment of the work of biochemists when work involving complex biochemical investigations is published.

It is obvious that one man alone cannot now combine the expertise of the laboratory with that of the ward and operating-theatre. In spite of this, many papers are published in which extensive laboratory work, often involving skills of a high order, is included without acknowledgment. May I state briefly what seem to me to be suitable conventions?

(1) Inclusion of general laboratory findings to complete the picture, or of minor routine, does not need acknowledgment.

(2) If the analytical work is of a special kind, then irrespective of the relevance of the figures to the topic under discussion, the analyst must be mentioned.

(3) Where the original work published is mixed and involves both the medical and chemical disciplines the clinician and the analyst should be joint authors.

These conventions, applied as a matter of courtesy between colleagues, contribute materially to professional harmony and ultimately to the better attainment of our aim of helping the sick.

Swansea. E. B. LOVE.

PSYCHIATRIC ASPECT OF ACUTE PORPHYRIA

SIR,—The cases Dr. Cashman reported (Jan. 14) were instructive; he concludes, basing this conclusion partly on the work of Gillhespy,[1] that "it seems generally agreed that E.C.T. is contraindicated in porphyria".

The following case is of interest in this connection.

A man of 30, whose younger brother had had acute intermittent porphyria for some years, had been having recurrent attacks of endogenous depression since the end of the '40s. In 1954, during one of these attacks, he tried to commit suicide with barbiturates.

In 1959 he began to get episodes of pain in the abdomen, back, and limbs. During these episodes, his urine became darkly coloured and was found to contain large amounts of porphobilinogen and δ-aminolævulic acid. This was reliable evidence of acute intermittent porphyria. In 1960 the patient had occasional attacks of pain, and chlorpromazine was given. By the autumn of that year the attacks became more and more frequent, until finally one attack shaded into the next. Pain was very severe; and on several occasions he was treated at a medical clinic.

The depressive symptoms came on gradually. In January, 1961, he made a serious attempt at suicide, and was sent to a psychiatric clinic. He proved to have the classical symptoms of endogenous depression. Some days before he had had an attack of porphyria, and during the first few days after admission he complained of pain in the arms and legs. He was emaciated and tremulous because of general muscular weakness. The result of a Watson-Schwartz test on the first day was positive.

He required E.C.T., but we hesitated to give it in view of his porphyria. After consulting Prof. J. Waldenström, and since it was regarded as life-saving, E.C.T. was started. He was given it 4 times.

The results were very good. The depressive symptoms disappeared completely within a fortnight, and so did his pain. He has had no attacks of porphyria since, which is remarkable as previously the attacks had been very frequent.

He has now been under observation for 2 months and is completely healthy and has returned to work.

I do not, of course, mean to assert that E.C.T. has a therapeutic effect in acute porphyria; but this case provides no evidence that E.C.T. will precipitate attacks of porphyria, as other workers have suggested.

The practical question of whether to give a patient with porphyria E.C.T. will often arise; and we hope our experience in this case may be helpful.

University of Gothenburg Psychiatric Clinic, Sahlgrenska Sjukhuset, Gothenburg, Sweden. M. B. HOLMBERG.

1. Gillhespy, R. O. *Lancet*, 1954, i, 908.

DYSPNŒA DUE TO SUBCLINICAL AMŒBIASIS

SIR,—In reply to Dr. Elsdon-Dew's letter of March 11, we regret we are unable to explain the mechanism by which *Entamœba histolytica* caused the chest symptoms of our patient. We assumed it to be an allergic phenomenon; relief of symptoms followed treatment of the amœbic infection and this relief has now been maintained for over two years.

Chest Clinic, St. Margaret's Hospital, Epping. IAN HAMILTON URSULA LUTWYCHE.

RENAL-ARTERY OBSTRUCTION

SIR,—Your annotation of March 11 points out the need for simpler methods to distinguish hypertension caused by unilateral kidney disease, but fails to mention the radioisotope renogram. Certain difficulties with the renogram have prevented more widespread trial. For the most part, these difficulties have been overcome. Recent changes which make it more reproducible and sensitive deserve comment, since it is potentially the simplest procedure for screening hypertensive patients.

Every technique used at present for detecting unilateral kidney disease has its special problems. The intravenous pyelogram is relatively insensitive to kidney-blood-flow differences. The aortogram is a somewhat hazardous hospital procedure unsuitable for screening large numbers. The test described by Howard et al.[1] is useful, but even modified and simplified[2] it is not suitable for the routine screening of non-selected hypertensive patients.

The radioisotope renogram theoretically provides a direct and sensitive comparison of blood-flow to the kidneys, and has the additional advantages of being simple, rapid, and atraumatic. This test was first described by Taplin et al.[3] in 1956, and was subsequently popularised by Winter[4] and others. Graphs of radioactivity are detected externally from each kidney area after the intravenous administration of a tracer substance. The problems involved in obtaining reproducible information by this method were quickly evident, and led Dollery[5] to conclude that it was "unsuitable as a screening test". He suggested, however, that it was "quite possible that the use of other chemical compounds or alteration in technique might surmount some of these difficulties . . ."

Three recent changes in the test have now improved its reproducibility and sensitivity: use of a radioactive substance which is removed from the blood only by the kidneys; of a collimator system which minimises geometrical differences; and of the prone position.

The radioactive test agent now used is ^{131}I-labelled sodium iodohippurate ('Hippuran').[6] In man, this substance is not taken up by the liver, and this avoids the skewed right curve which plagued the use of ^{131}I 'Diodrast'. Since it is removed from the blood almost completely by the kidney, its rate of extraction correlates with kidney blood-flow, which is the major factor we are trying to measure.

1. Howard, J. E., Berthrong, M., Gould, D. M., Yendt, E. R. *Bull. Johns Hopk. Hosp.* 1954, **94**, 51.
2. Rapoport, A. *New Engl. J. Med.* 1960, **263**, 1159.
3. Taplin, G. V., Meredith, O. M., Jr., Kade, H., Winter, C. C. *J. Lab. clin. Med.* 1956, **48**, 886.
4. Winter, C. C. *J. Urol.* 1956, **72**, 182.
5. Dollery, C. T. *Proc. R. Soc. Med.* 1960, **53**, 969.
6. Nordyke, R. A., Tubis, M., Blahd, W. H. *J. Lab. clin. Med.* 1960, **56**, 436.

Having such a test agent allows certain changes in renogram instrumentation which markedly increase the test's reproducibility. These include wide collimation aimed directly at the kidneys, and withdrawal of the crystal at least 15 cm. from the skin surface. Each of these innovations reduces the effect of differences in kidney position and interposing tissue. In addition, the patient is placed prone, a position in which the kidneys have little tendency to shift.

A previously promising, but difficult, test has thus been made simple, reproducible, and sensitive. The problems met by Dollery and others have been largely overcome. If this technique continues to prove as accurate as the Howard test in distinguishing unilateral disease, it will have the advantage of being the first truly simple screening test for unilateral kidney hypertension.

Straub Clinic,
Honolulu, Hawaii. ROBERT A. NORDYKE.

POSSIBLE TERATOGENIC EFFECT OF TOLBUTAMIDE IN THE PREGNANT PREDIABETIC

SIR,—In their article, Dr. Larsson and Dr. Sterky [1] described the possible teratogenic effect of tolbutamide in a young pregnant prediabetic patient who was delivered spontaneously and prematurely, and gave some experimental evidence in support of this hypothesis.

It is well known that congenital anomalies are more frequent in children of pregnant diabetics, whether receiving insulin therapy or not, than in non-diabetics. But I should like to report briefly 20 cases, and some experimental trials, where cardiac abnormalities were not observed.

Although the oral therapeutic dose of tolbutamide for man is approximately 25 mg. per kg. body-weight, Bänder [2] observed no pathological change in blood, liver, kidneys, heart, and other organs in dogs receiving 100 mg. daily per kg., and in rats receiving for nine months 1000 mg. daily per kg. This period of administration is equal to the period of gestation.

Sugar [3] reported on 1 pregnant diabetic receiving carbutamide who carried successfully to term and bore a healthy child. Lass [4] described a pregnant diabetic who was delivered in a precomatose condition—after influenzal pneumonia during the seventh and eighth month of pregnancy while on carbutamide. Necropsy of the stillborn child did not reveal the cause of death. The fœtus was normally developed and cardiac anomalies were absent. El Badry [5] and Moss et al.[6] reported the control of 3 pregnant diabetics until full term by tolbutamide, when 3 normal babies were born.

Early in the sulphonylurea era, in 1956 and 1957, we gave carbutamide to 4 pregnant diabetics (a total dose of 75–417 g. over periods ranging from one to five months [7]). 3 full-term vaginal deliveries were achieved, without maternal or fœtal complications. The babies have remained healthy and non-diabetic. The 4th patient was delivered prematurely (thirty-fourth week) of a macerated fœtus with a prolapsed cord. This patient needed a big dose of 75 g. carbutamide during the sixth month of pregnancy; and it was then withdrawn because her carbohydrate tolerance had become normal. She received the drug for only thirty days.

Since 1957, tolbutamide, which is reasonably safe, has been administered (1–1·5 g. daily), as soon as lowered glucose tolerance has been detected, to selected pregnant diabetics; and we reported the follow-up of another 8 pregnant diabetics who had normal, healthy babies,[8] with 1 exception. This baby died suddenly, thirty hours after labour, but necropsy was not possible; its mother had had placenta prævia, and was delivered prematurely by forceps. In 5 of our cases followed during the next pregnancy, tolbutamide maintained normoglycæmia in 2; 2 needed the synergistic effect of 75 g. phenformin begun at the fifth and seventh month respectively; and in the 5th there was secondary failure from the fifth month of gestation onwards and insulin was needed.[9] In five years we have observed no cardiac abnormalities in these 15 babies.

Taking all cases together, including Larsson and Sterky's, there was 1 cardiac anomaly among 21 children whose mothers received sulphonylurea to control diabetes during pregnancy. The pancreas of the 2 cases studied at necropsy was normal and the usual β-cell hyperplasia was not seen. We have noted with sulphonylurea therapy that the fœtus tends to be of normal size.

Though insulin remains the orthodox therapy for pregnant diabetics, tolbutamide may have a place when the giving of insulin is not possible or not tolerated. We select only those with a good response to the acute (1 g.) four-hour test,[10] and in preference those whose carbohydrate tolerance decompensates only during pregnancy and who are almost non-diabetic between pregnancies.

Unger et al.[11] considered the giving of tolbutamide in the tolbutamide-responsive subgroup of diabetics highly physiological, since the drug, in their opinion, permits a normal insulin output from a hyporesponsive β-cell.

Faculty of Medicine,
Alexandria University,
Egypt, U.A.R. M. H. GHANEM.

"OPEN TO DOMINION GRADUATES ONLY"

SIR,—Your issue of May 6 contains an advertisement for a senior surgical registrar post "open to Dominion graduates only". I know of one other post which is regularly advertised in this way, and there may well be more. I am sure that my Commonwealth friends will not misunderstand me when I say that this form of advertisement causes much concern.

Many will see the viewpoint of the management committee as follows: it is not always easy to find good men at registrar level to do the routine surgery at a peripheral hospital, and it is tempting to upgrade the post in order to attract an experienced man from the Commonwealth who will not prove an embarrassment by expecting a consultant post at the end of his tenure. But this is not an answer to the problem of hospital staffing, it is a makeshift expedient, and it raises an important point of principle which should not go unchallenged.

Consider the facts. There is a great deal of surgery waiting to be done in this country, as shown by hospital waiting-lists. There is a correspondingly large number of fully-trained surgeons who are eager to do it. These are the men who in their professional prime are given the farcical title of "time-expired" senior registrars, and lead a precarious episodic existence from locum to locum and from interview to interview. Something, whether it be political, administrative, or financial, is keeping these patients and these surgeons apart. I am not going to suggest what this is, but clearly here is a problem to be solved, not evaded. Now consider this advertisement—here is a hospital of good repute in a pleasant district which requires the services of an experienced surgeon with a higher degree to whom they are prepared to pay up to £2000 a year. If a man of this calibre is needed then why not spend a little extra and appoint a consultant? I know of several senior registrars from teaching hospitals who would be only too thankful to take up such a post immediately.

The regional boards and the Ministry have apparently not grasped that there is actual unemployment among fully-trained hospital specialists; this is partially concealed by the creation of temporary clinical assistantships and the manipulation of research funds, but what a tragic

1. Larsson, Y., Sterky, G. *Lancet*, 1960, ii, 1424.
2. Bänder, A. *Dtsch. med. Wschr.* 1959, **84**, 996; *Germ. med. Mon.* 1959, **4**, 373.
3. Sugar, S. J. N. At the session of the New York Academy of Sciences; Feb. 15, 1957.
4. Lass, A. *Geburtsh. u. Frauenheilk.* 1958, **18**, 1167.
5. El Badry, A. *J. Egypt. med. Ass.* 1958, **41**, 106.
6. Moss, D. M., De Lawter, D. E., Canary, J. J. *Ann. intern. Med.* 1959, **50**, 1408.
7. Ghanem, M. H., Mikhail, M. N. *Alexandria Med. J.* 1957, **3**, 383.
8. Ghanem, M. H. *ibid.* 1960, **6**, **14**.
9. Ghanem, M. H. *Chemotherapia, Basel*, 1961 (in the press).
10. Ghanem, M. H., Mikhail, M. N. *Lancet*, 1956, ii, 514, 898.
11. Unger, R. H., Madison, L. L., Caster, N. W. *Ann. N.Y. Acad. Sci.* 1959, **82**, 570.

misapplication of talent! Imagine the reactions of a trade union if, at a time when there was unemployment in certain skilled grades, it was proposed to bring in Commonwealth labour in order to keep down the wages bill. They would not stand for it and neither should we.

SURGICAL REGISTRAR.

LEUKÆMIA ASSOCIATED WITH MONGOLISM

SIR,—In their recent paper, Miss Tough and her colleagues (Feb. 25) drew attention to the fact that most cases of chronic myeloid leukæmia are associated with the Ph[1] chromosome, an abnormal small acrocentric chromosome (probably no. 21) formed as a result of either a deletion or translocation. They also observed that mongoloids are trisomic for what is probably the same chromosome, and that acute leukæmia is more likely to develop in mongols. They postulated as a working hypothesis that a locus controlling leucopoiesis was present on that chromosome, and that triplication of the locus increased the liability toward acute leukæmia, while a deletion or translocation involving the locus was associated with chronic myeloid leukæmia. Baikie et al.[1] had noted previously that the probability of acute leukæmia (but not apparently chronic myeloid leukæmia) was greater in mongoloids.

Stewart [2] concluded that leukæmia associated with mongolism was of a variety which she classified as prezygotic—i.e.,

NUMBER AND INCIDENCE OF PATIENTS WITH COEXISTENT MONGOLISM AND LEUKÆMIA BY AGE-GROUPS, PENNSYLVANIA, 1955–59

Age (yr.)	Total cases of mongolism and leukæmia*		Cases of mongolism and leukæmia in institutions*		Leukæmia
	Observed	Expected†	Observed	Incidence per 10^5‡	Incidence per 10^5§
0–9	8	0	4	298·00	4·47
10–19	6	0	4	258·00	2·18
20–29	1	0	1	106·60	1·83
30–39	3	0	3	404·80	2·61
40–	3	2	3	672·60	12·42

* Coexistent cases found in our review of all leukæmia-death certificates.
† Mongoloid population-at-risk based on birth frequency and life table of Carter [3] to age 10, assumption of normal life-expectancy over 10 years of age, and Pennsylvania population data.§
‡ Mongoloid population-at-risk estimated from our survey of public and private institutional censuses, 1955 to 1959.
§ Total population-at-risk estimated from data supplied by division of statistics and records, Pennsylvania Department of Health.

due to the inheritance of a gene, mutated before conception, which produces premalignant changes in ancestral cells of the reticuloendothelial system, and a peak incidence of the disease between the second and fifth years of life. She considered that the malignant cells were nongranular (often called lymphoblasts or monoblasts), but were probably derived from undifferentiated stem-cells. This contrasts with the postzygotic leukæmias, in which the original mutation occurs in the somatic cell, and the disease generally appears later than the age of five years, is not associated with mongolism, and is manifested by the appearance of cancer cells of a relatively mature form.

Our findings are somewhat different. They were made during a recently completed investigation of the relationship between mongolism and leukæmia which will be reported in detail elsewhere. One phase of the study was an analysis of the incidence of leukæmia in mongolism at all ages, rather than in the mongoloid-child population alone. Death certificates of all who died of leukæmia in the state of Pennsylvania during the five-year period 1955-59 were examined. The results are summarised in the accompanying table. 21 cases of coexistent mongolism and leukæmia were discovered. A raised incidence of leukæmia in mongolism was demonstrated at all ages. 5 of the 21 cases had been diagnosed as having chronic forms of leukæmia; 3 of these were granulocytic and 2 were lymphocytic. 4 of the 5 chronic cases were patients over the age of 30.

In this study we were able to carry out hæmatological investigations, including cytogenetic analyses, in 3 patients with mongolism and acute leukæmia. Our findings agree with those of Tough et al. in that the only consistent abnormality has been typical of mongolism itself, and that the blood and bone-marrow cells of these patients have proved easier to prepare for cytogenetic analysis than those of other leukæmic patients. Although we have noted occasional additional chromosomal aberrations, their inconstancy, and our present inability to identify the dividing cells make it premature to draw any general conclusions. It would be of great interest to perform cytogenetic analysis on patients with coexistent mongolism and chronic granulocytic leukæmia.

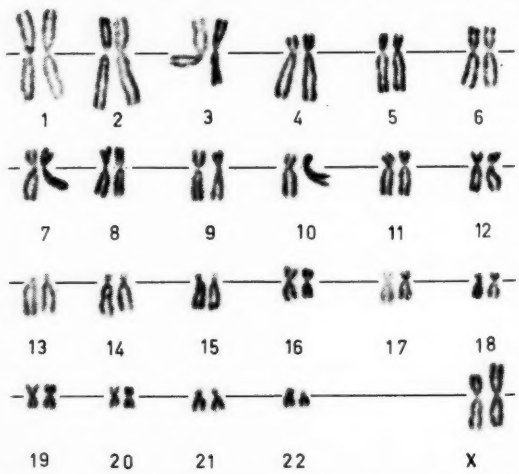
N. WALD
W. H. BORGES
C. C. LI
J. H. TURNER
M. C. HARNOIS.

University of Pittsburgh
Graduate School of Public Health
and School of Medicine,
Pittsburgh, Pennsylvania.

1. Baikie, A. G., Court Brown, W. M., Buckton, K. E., Harnden, D. G., Jacobs, P. A., Tough, I. M. *Nature, Lond.* 1960, **188**, 1165.
2. Stewart, A. *Brit. med. J.* 1961, i, 452.
3. Carter, C. O. *J. ment. defic. Res.* 1958, **2**, 64.

NEW TYPE OF CHROMOSOMAL MOSAICISM IN OVARIAN DYSGENESIS

SIR,—In a preliminary report, Fraccaro et al.[1] demonstrated an abnormal chromosome in three sex-chromatin-positive patients with the clinical diagnosis of the Turner syndrome. Cells from skin and bone-marrow continuously grown in vitro had 46 chromosomes, but 1 chromosome was abnormal. This was metacentric, and of the same size, approximately, as no. 3 (standard nomenclature). The abnormal chromosome was interpreted as an isochromosome for the long arm of X, but other possibilities were not excluded. If this hypothesis is correct, these individuals have trisomy for the long, and monosomy for the



short, arm of X. Monosomy for the short arm might therefore be the important factor in the ætiology of ovarian dysgenesis.

A similar situation was recently found by Blank et al. (April 29) in another sex-chromatin-positive patient with the Turner syndrome. In this case, however, 10% of the cells examined (cultured leucocytes) had 45 chromosomes, and a sex-chromosome constitution of the XO type.

1. Fraccaro, M., Ikkos, D., Kaijser, K., Lindsten, J., Luft, R. *Lancet*, 1960, ii, 1144.

I have examined the chromosomes of two further sex-chromatin-positive patients, with the clinical diagnosis of ovarian dysgenesis. One of them was colour-blind. Leucocytes derived from peripheral blood were cultured by a modification of the technique of Hungerford et al.[2] Most of the cells (70–80%) from both patients had 46 chromosomes, but the rest only 45. A careful analysis of several metaphases with 46 chromosomes showed that they had the same abnormal chromosome as described above (see figure). All cells with 45 chromosomes had a karyctype of the XO-type. This is strongly suggestive of a mosaic of two cell types in the leucocytes of these patients.

These findings confirm our earlier results, and it seems clear that there is a variant within the syndrome of gonadal dysgenesis, consisting of sex-chromatin-positive individuals with an isochromosome for the long arm of X. They also indicate, as in the case of Blank et al., that a proportion of these individuals are probably mosaics of the type XO isochromosome X.

Department of Endocrinology and Metabolism, Karolinska Sjukhuset, Stockholm, Sweden. J. LINDSTEN.

OBSERVATIONS ON SATELLITED HUMAN CHROMOSOMES

SIR,—We should like to make a few comments on the brilliant paper by Dr. Ferguson-Smith and Dr. Handmaker (March 25).

The satellite association described in the paper has also been reported by Harnden.[3] As our attention has also been focused on the phenomenon, we are able to confirm the findings, as we have observed the same associations in squash preparations from long-term tissue cultures of bone-marrow cells (unpublished).

As for the number of satellites in human cells, we feel it would be of general interest to answer the following questions:

(1) How many of the satellites come within their definition of "a secondary constriction with distinct chromatin knobs projected from the arms on slender stalks", and how many were only seen as "negative heteropyknosis at the ends of the chromosome arms"?

(2) Were 10 satellites found in any of the 250 cells examined when only the former definition of a satellite is used and negative heteropyknosis is excluded?

(3) Were 5 or 6 satellites found in the group-IV chromosomes in any cell if negative heteropyknosis is excluded?

Using the first definition of a satellite, at least 7 satellites can be found in a single cell, as shown in the accompanying photograph of a bone-marrow cell of a normal male. All 4 small acrocentrics in group VII have satellites and at least 3 (possibly 4) of the chromosomes in group IV are satellited. The remaining 2 chromosomes in group IV show no evidence of satellites, but 1 of them is so close to other chromosomes that it cannot be seen clearly.

Institute of General Pathology, University of Aarhus, Denmark. G. BRUUN PETERSEN
A. J. THERKELSEN.

2. Hungerford, D. A., Donelly, A. J., Nowell, P. C. *Amer. J. hum. Genet.* 1959, **11**, 215.
3. Harnden, D. G. *in* Recent Advances in Human Genetics (edited by L. S. Penrose); p. 32. London, 1961.

LABELLING OF MEDICINES

SIR,—As one of the doctors who (together with a pharmacist) recently discussed this problem with Lord Archibald, I wish to support Professor Wilson's viewpoint (May 20).

For some two years I have been increasingly concerned with the great difficulty in identifying dispensed medicines and tablets. In 1960, I suggested[1] a scheme for tablet identification. After high-level discussion in the Association of British Pharmaceutical Industry, the Pharmaceutical Society, and the British Medical Association, the B.M.A. decided to support my scheme (despite the implications that it might increase the drug bill) and they referred it to the Pharmaceutical Standing Advisory Committee of the Central Health Services Council, urging them to implement it.

If a decision is made to implement a scheme for identifying tablets (which is unlikely in view of the concern about rising drug costs) there will inevitably be delay. Because my scheme covers only solids, and does not include liquid medicaments and ointments, I think the profession should agree in principle that all containers of dispensed medicines and tablets should be labelled with the name of the drug, unless the prescriber expressly gives instructions to the contrary.

As a general practitioner who works both in hospital and outside, I have experienced the difficulties Professor Wilson mentions in recognising drugs (particularly in general practice with locum, partnership, and holiday arrangements, though I am pleased to note that an increasing number of hospitals label containers).

The Joint Formulary Committee's recent statement on this topic needs reconsidering, because their suggestions are both time-consuming and impracticable. Coupled with the proposal by the Ministry to limit the prescribing space on an E.C. 10, having to write the name twice is going to cause inconvenience, particularly when more than one item is prescribed.

I suggest that in future the words "Nomen proprium all items please" should be printed on form E.C. 10, and that, unless these words are deleted by the doctor, the identity of the drug should appear on the container. I have this working stamped on all my prescriptions, and this works very well in practice. Many patients nowadays want to know what they are taking and of course read their prescriptions. It is only exceptionally that the name of the drug should be omitted—e.g., in alcoholism, carcinomatosis, and psychoses.

The outlook of many of the professions' representatives is not as realistic as Professor Wilson's. This is all the more regrettable because the Government's very proper attitude is that this is entirely a professional matter.

London, W.12. JOHN D. W. WHITNEY.

SIR,—I strongly endorse Professor Wilson's case (May 20) for improving the labelling of drugs dispensed to patients.

Many patients attending this hospital are receiving treatment for conditions unrelated to their eye diseases. When admitted to hospital these patients bring assorted boxes and bottles containing a few tablets. These are handed to the ward sister with the phrase, "My doctor says I must take the tablets regularly".

Usually the patient's own supply runs out before they leave the hospital; this entails extra work for doctor, sister, and pharmacist, in an attempt to ascertain the correct names of the drugs.

All drops, ointments, and other drugs dispensed at this

1. Whitney, J. D. W. *Brit. med. J.* 1960, i, 50.

hospital have an easily recognisable abbreviated name printed on the label. This could easily be extended to other branches of the dispensing service.

The patient is not really worried about the writing on the label as long as he receives benefit from the drug.

Manchester
Royal Eye Hospital. W. S. FURNISS.

21-YEAR SURVIVAL AFTER REMOVAL OF WILMS TUMOUR

SIR,—The prognosis of Wilms tumour has now definitely improved, although mortality is still high. This tumour is important in childhood because it makes up 20% of the total neoplasms, as against 0·5% in adults. The case reported here is noteworthy because full recovery took place.

A boy, aged 2 years, was admitted to this department in April, 1940, with anorexia, cough, and abdominal symptoms. A tumour the size of a fist was palpated in the abdomen. Because he had intercurrent influenza with complications, operation had to be postponed until the end of July, 1940, when the left kidney, which contained a tumour, was removed. Microscopic examination revealed a Wilms tumour. Post-operatively the patient was irradiated, receiving a total of 4788r. Recovery was uneventful; and at subsequent follow-up he had no symptoms.

Eight years after this operation the patient was again admitted, this time with acute nephritis. Recovery was rapid; two months later his tonsils were removed.

Recently the patient again reported for examination. He is now 23 years old, in perfect health, working as a clerk, and even taking part in sports. The original slides prepared from the specimen removed 21 years ago were re-examined; and the original diagnosis has been fully confirmed.

1st Department of Pædiatrics,
University Medical School,
Budapest. Z. ERDŐS.

A MODIFIED PERITONEOSCOPE

SIR,—I have devised a modified peritoneoscope which may be of interest to other surgeons.

It consists of a hollow metal tube ending in a wire-cage of flexible steel wires coated with nylon. Between these wires is a mesh-work of fine nylon to prevent the viscera or omentum from prolapsing between the bars of the cage and being crushed. The folded cage is introduced into the abdomen through a small incision. Then it is opened out (see accompanying figure) thus separating the viscera and bringing them within the focal range of the telescope; and they can then be examined. The telescope with the lamp is introduced through the tube. I have carried out many experiments in the faculty of medicine of Cairo University, both in the postmortem room and on dogs.

The advantages of the modified peritoneoscope are as follows:

(1) With the standard apparatus, air injected into the peritoneal cavity cannot be directed into the recesses which need exploring. Thus only part of the anterior surface and anterior border of the liver, and a small part of the fundus of the gallbladder, the lower border of the spleen, and part of the anterior surface of the stomach between them can be seen. Some coils of intestine covered with omentum and some areas of the colon are also visible. By putting the animal in the Trendelenburg position, the gut falls away from the pelvis and then some of the pelvic organs, such as the posterior surface of the bladder, the upper border of the uterus, and the anterior surface of the pelvic colon, can sometimes be explored.

The modified apparatus can be insinuated between the diaphragm and the liver, and between the liver and adjacent viscera. Thus the whole peritoneal surface of the liver—both diaphragmatic and visceral—can be explored. The whole peritoneal surface of the gall-bladder from neck to fundus is visible. Much more of the spleen and anterior surface of the stomach can be seen. The instrument can be pushed into the subhepatic space and in dogs the kidney surface can be seen. Moreover, the apparatus can be passed along the ascending colon to the cæcum. By elevating the foot of the table, the instrument can be passed into the pelvis and all the pelvic organs—bladder and pelvic colon, and, in women, uterus, fallopian tubes, and ovaries—can be examined.

(2) In the original peritoneoscope, the telescope with the lamp cannot be brought near the viscera in case it gets soiled, and the view becomes indistinct. But with the modification the viscera are separated and held at the focus of the telescope. The organs are thus more highly magnified and clearer.

(3) Since the viscus being examined is fixed by the expanded cage, manipulation is easier with the modified apparatus. Cholecystography or biopsy have been more successful.

I hope that some established instrument-maker may be interested in developing the instrument. This could lead, I believe, to much more general use of peritoneoscopy.

Cairo,
United Arab Republic. ADLY I. FAHIM.

MENTAL DISEASE AFTER OPERATIONS FOR MITRAL STENOSIS

SIR,—Major mental disorders, including psychoses, have recently been reported as a complication of mitral commissurotomy. Such disturbances are apparently more common after mitral surgery than after other major operations, and it has been suggested that cardiac surgery might cause more stress to patients with chronic rheumatic heart-disease than to others,[1] or the very thought of an operation on the heart might give rise to greater anxiety than operations on other organs.[1 2]

We tried to assess another factor—the significance of preoperative personality—in relation to heart surgery; and we studied a consecutive series of 61 patients who had undergone mitral surgery.

In this series of 61, 3 became psychotic soon after their operation. This figure thus appears to confirm the earlier reports [1 3 4] that major mental disorders are common after commissurotomy. But the frequency of major mental symptoms before operation was also high: 5 patients (including 2 of the 3 above) had had episodes of disorientation, delusions, and/or hallucinations, usually with amnesia for at least a few days—in fact, organic psychoses. Another patient had had severe chronic depression and repeatedly attempted suicide. 4 of these 6 had been inpatients in mental hospitals.

The high incidence of mental disease observed suggests that patients in this series may be more predisposed to mental disease than the average. The psychotic picture before operation did not differ from that after operation. It may therefore be assumed that the operation as such was not responsible for the postoperative psychosis or, in other words, that the frequency of psychoses after the cardiac operations would not have increased if the patients had had a normal mental make-up before.

The frequency of rheumatic fever, chorea, and cerebral symptoms of arterial embolism in the mentally affected was the same as in the other cases. In nearly all 6 patients

1. Bliss, E. L., Rumel, W. R., Branch, C. H. H. *Arch. Neurol. Psychiat. Chicago*, 1955, **74**, 249.
2. Boss, M. Einführung in die psychosomatische Medizin. Berne, 1954.
3. Fox, H. M., Rizzo, N. D., Gifford, S. *Amer. Heart J.* 1954, **48**, 645.
4. Kaplan, S. M. *Psychosom. Med.* 1956, **18**, 221.

with preoperative mental disease this seemed to have arisen in previously disturbed personalities. This might suggest an early cerebral injury of rheumatic type predisposing to mental disease, or a joint predisposition to mental and cardiac disease.

Department of Neurology, SVEN J. DENCKER
Department of Psychiatry, University of Lund, Sweden. ARNE SANDAHL.

HOSPITAL DOCTORS

SIR,—I welcome the proposals of the Platt Working Party to create the post of " medical assistant ".

Most of my experience in England was in the casualty and accident service, which work I thoroughly enjoyed, although the premises and consultant supervision left much to be desired. In view of the recent report of the Nuffield Trust it might be asked why I left the accident service, and England. I could see no future for myse f in the National Health Service in its existing framework. Firstly, the road to a consultant appointment appeared too formidable, I have never found examinations easy, and the primary F.R.C.S. had to be abandoned for several reasons. Secondly, I did not have a teaching-hospital registrar appointment, nor was I likely to get one.

The apparent future offered nothing but a series of senior-registrar appointments with all their frustrations and uncertainties.

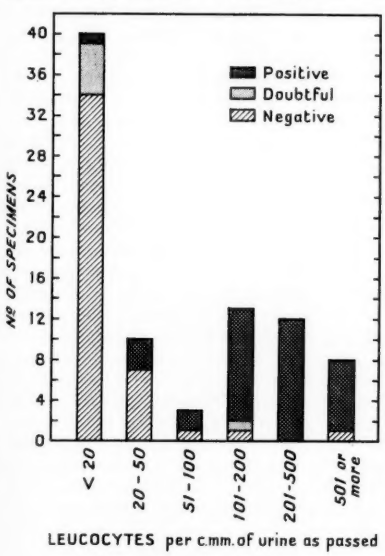
Not all registrars wish to become consultants and many would welcome the opportunity of carrying on their work provided they were given security of tenure. I came abroad, while several of my colleagues have drifted into other permanent appointments.

I believe that the standard of the Hospital Service would be improved by creating " medical assistants ".

Medical Department,
Gombe,
Northern Nigeria. EDWIN J. WRIGLEY.

DETECTING PYURIA IN GENERAL PRACTICE

SIR,—In this country nowadays many of us in general practice enjoy access to prompt and effective laboratory facilities. Yet there is still a rich harvest of immediate diagnostic information to be reaped by microscopy of the urine, for which there is no satisfactory alternative. A drop from an ordinary specimen is sufficient; it is placed on a slide and examined unstained under the $^2/_3$ in. and $^1/_6$ in. objectives without a coverslip.



Leucocyte-counts of urine.

In 100 consecutive specimens examined thus in ordinary practice, pyuria was by far the commonest abnormal finding, and was noted in 27. On testing by boiling and acidification protein was found in only 16 of these 27; it is especially in the somewhat turbid pyuric urines that detecting small traces of protein is difficult. Filtration is tedious, and may seem superfluous to a receptionist undertaking routine testing.

Another relevant test consists in adding about a third of its volume of 10% potassium-hydroxide solution to about an inch and a half of urine in a boiling tube. Purulent urine then becomes viscous, which may be demonstrated by pouring it out, or more readily by shaking it and observing how slowly the bubbles rise. This test is helpful, but may inexplicably not reveal severe pyuria; the results of testing 87 samples on which leucocyte-counts were made are shown in the accompanying figure.

A neat biochemical test for peroxidase in urine has been described [1]; but it is positive in the presence of either red or white cells, and is relatively time-consuming.

Microscopy can usually be very speedily carried out if the equipment is to hand—about as quickly as testing for protein by boiling—and is particularly useful for diagnosing urinary infections in young children, in whom the illness may be acute, the history non-specific, and the amount of urine obtainable very small.

I wish to thank Dr. Rosemary Biggs for some of the leucocyte-counts, and Dr. Ian Skinner, who taught me the potassium-hydroxide test.

Calverton,
Nottingham. J. M. FORRESTER.

PAVLOV OR FREUD?

SIR,—It seems necessary to point out to those among your correspondents who plead for a rapprochement between psychotherapy and behaviour therapy (Dr. Bower, April 1; Dr. MacDonald, April 22) that they misunderstand the position taken up by the proponents of the latter. Not only has behaviour therapy been invented with the aim to supersede psychotherapy but the two also lack common ground.

Psychotherapy recognises mind as an entity, behaviour therapy does not. Where there is no room for mind there can, of course, be no question of diseases of the mind, and, consequently, no psychopathology. Inquiries addressed to learning theorists about psychopathological issues involved in their cases (Dr. Bower, April 1; Dr. Edelston, May 6) are therefore out of place. Professor Eysenck is quite explicit on these points. In a paper dealing with neuroses and their treatment [2] he says: " Throughout this paper I have stressed entirely the treatment of *symptoms* without alluding to any underlying *complex* or illness. The reason is that *as far as learning theory is concerned there is no illness and there is no complex*. We are dealing entirely and exclusively with maladapted habits formed through a process of conditioning . . ." (Professor Eysenck's italics.) In another place [3] Professor Eysenck commits himself to the following view: " If the physical causation of G.P.I. and similar diseases had been known from the beginning, it is doubtful if these would have been classified as psychiatric disorders." Although this view removes insanity from the scope of the psychiatrist the underlying thinking is logical, coming from one for whom mind is non-existent.

As far as I can follow Professor Eysenck's basic thinking, he makes use, on the one hand, of the concept of neural properties inherent in the autonomic and other parts of the nervous system and, on the other, of the concept of outer stimuli or patterns of stimuli impinging upon it. There is nothing else. The interaction of the two brings about the conditioned responses or, in behavioural terms, the habits. I do not see how this theoretical outlook can invoke Pavlov's work for its basis. If we take the classical salivation experiments, neither the conditioned nor the unconditioned stimuli can be said to have brought about the salivation. The salivation was brought about by hunger, in animals kept without food and made to expect nourishment in certain experimentally defined circumstances.

1. Järvinen, K. A. J. *Brit. med. J.* 1958, i, 379.
2. Eysenck, H. J. *Proc. R. Soc. Med.* 1960, **53**, 507.
3. Eysenck, H. J. Handbook of Abnormal Psychology; p. 4. New York, 1961.

In other experiments analogous inner sources propelling the responses must be postulated. And the same, of course, applies to "habits" of man. But this side of the picture appears blotted out in learning theory. In the cases recently published by adherents of behaviour therapy no attempt is made to uncover from what inner sources the habits of their patients have arisen and continued to be fed; not to speak of the tracing of conditioning influences which seems far less than convincing. And yet, the whole procedure ranks as ætiological within the meaning of learning theory.

Lastly, a word about the transvestite treated by Dr. Barker et al. (March 4). In their comments the authors seem distinctly uneasy about what they have accomplished, and conclude their letter by saying, "at present we are unable to demonstrate the precise mechanisms which alleviated symptoms in our patient." They may perhaps be willing to accept that, shorn of all the medical trappings, what they have done was to submit their patient to a series of exquisite humiliations. Common sense understands if, as a sequel to this, he has given up his "bad habit", at least for the time being.

London, W.1. JOSEPH ZELMANOWITS.

SIR,—I have waited in vain for someone else to emend an obvious error in the title of this recent correspondence. Surely—since we are discussing science, not religion or palmistry—it should read Pavlov *and* Freud?

Loughton, Essex. ALEX COMFORT.

SERUM-LACTIC DEHYDROGENASE IN DIAGNOSIS OF MYOCARDIAL INFARCTION

SIR,—Estimation of the serum-glutamyl-oxaloacetic-transaminase (S.G.O.T.) has been widely used in the past three or four years for diagnosing myocardial infarction. Now serum-lactic dehydrogenase (S.L.D.H.) estimation is being used more and more.

The medical firms at this hospital have been performing this test, in the past six months, together with the S.G.O.T. estimation, and I have compared the relative value of these two investigations in diagnosing myocardial infarction.

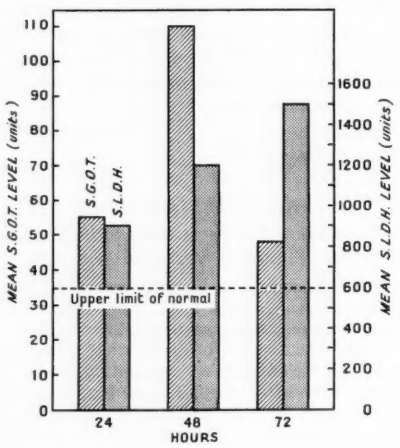
The graph is based on 45 S.L.D.H. estimations and 45 S.G.O.T. estimations on specimens from patients with myocardial infarction obtained within 72 hours of their admission to hospital. The 3 large groups are based on levels of circulating enzymes during the first, second, and third 24-hour period in hospital.

I took as the upper limits of normal 35 Sigma Frankel units for S.G.O.T., and 600 Berger & Broida units for S.L.D.H.; in the first 24-hour period the mean levels of both enzymes rose to about 150% of their upper normal levels. During the second 24-hour period the mean S.G.O.T. level rose to approximately 300% and the S.L.D.H. to 200%. In the third 24-hour period the S.G.O.T. fell to 140%, while the S.L.D.H. continued to rise to approximately 250%.

Thus both the S.L.D.H. and the S.G.O.T. levels rise rapidly during the first 24 hours, but whereas the former continues to rise slowly in the subsequent 24-hour periods, the S.G.O.T., after reaching a maximum in the second 24-hour period, commences to fall rapidly towards normal in the third.

For estimations carried out more than 72 hours after the onset of chest pain the S.L.D.H. appears the more satisfactory test.[1] Our results support these findings.

False negatives have been observed in approximately 9% of cases in which the S.G.O.T. alone was estimated.[2] We found in 45 estimations that the S.L.D.H. was raised to pathological levels on 7 occasions on which the S.G.O.T. remained within normal limits. But the S.L.D.H. cannot be assumed to be the more sensitive test on these grounds as even slight hæmolysis of the blood specimen will raise the S.L.D.H. appreciably, but the S.G.O.T. will remain unaltered. Erythrocyte-L.D.H. concentration is some hundreds of times greater than plasma-L.D.H. This is, therefore, a major source of error; and all specimens sent for S.L.D.H. estimation should be freshly taken and unhæmolysed.



S.G.O.T. and S.L.D.H. levels in the first three 24-hour periods after admission in patients with myocardial infarction. (Each based on 45 estimations.)

Both the S.G.O.T. and S.L.D.H. were estimated colorimetrically, and this takes 1½ to 2 hours. One of the reagents used for the S.L.D.H. test is reduced diphosphopyridine nucleotide, which is expensive: the materials for the S.L.D.H. test cost about 7*s.* compared with about 1*s.* for S.G.O.T. estimation.

North Middlesex Hospital, London, N.18. ROSS S. MELLICK.

1. King, J., Waind, A. P. B. *Brit. med. J.* 1960, ii, 1361.
2. Dewar, H. A., Rowell, N. R., Smith, A. J. *ibid.* 1958, ii, 1121.

BRONCHODILATORS AND CORTICOSTEROIDS IN ASTHMA

SIR,—We are writing to answer Dr. Gandevia's comments (May 13) on our paper.[1]

Firstly, concerning our criteria for labelling patients emphysematous, a reference was given in our paper to the work published by Dr. Thomson and Dr. Hugh-Jones.[2] They reported that serial one-second forced expiratory volume ($F.E.V._1$) and vital capacity (V.C.) tests before and after aerosol isoprenaline can differentiate between patients with pure asthma and those with asthma plus emphysema. Our patient B in fig. 2 (referred to by Dr. Gandevia) came into the latter category. The highest $F.E.V._1$ percentage of the V.C. that she has ever attained, during four years' treatment with corticosteroids, has been 56%. At this time her $F.E.V._1$ was 1720 ml., her V.C. 3030 ml., and her forced vital capacity 2800 ml., indicating obstructive disease with a good V.C.—i.e., absence of restrictive disease. We feel that it is justifiable to use the term emphysema for patients who show this type of ventilatory defect in the absence of bronchial narrowing which will respond to a bronchodilator.

We found that the group of patients who showed the haphazard response to bronchodilators (illustrated by our fig. 5), had advanced emphysema where bronchospasm coexisted as the less significant factor, in contrast to the type of disease referred to above. Attention was drawn in the test and the caption of the figure to the low ordinate scale which represents the degree of reversible bronchial narrowing. It is this group, as would be expected, in which we have found no improvement with corticosteroid therapy unless there has been some additional disabling factor—e.g., excessive mucoid sputum—which improved with drugs.

King Edward VII Sanatorium, Midhurst, Sussex. K. M. HUME
E. RHYS JONES.

1. Hume, K. M., Rhys Jones, E. *Lancet*, 1960, ii, 1319.
2. Thomson, W. B., Hugh-Jones, P. *Brit. med. J.* 1958, i, 1093.

DIABETES AND PRESCRIPTION CHARGES

SIR,—Sufferers from several chronic diseases who need constant drug treatment to maintain health or even life will suffer increased hardship from the doubled prescription charge, but none more than the severe diabetic, with his numerous needs at 2*s.* each item:

(1) Insulin (one or two types).
(2) Insulin syringe (B.S.1619).
(3) Needles (luer-mount).
(4) Spirit for sterilisation (" industrial " is best).
(5) Cotton wool (" hospital pack " is cheapest, and satisfactory).
(6) Tablets for urine testing.
(7) Sulphonylurea tablets.

Composite packs: (*a*) syringe and 2 luer-mount needles; (*b*) urine analysis set.

The Ministry has mitigated the hardship by announcing that the doctor, at his discretion, may prescribe items 1–7 for a long time—even up to three months—*irrespective* of the *quantity* ordered (and it is hard to imagine any reason for his not doing so). Some practitioners seem unaware of this permission and this letter is to publicise this fact.

For the information of diabetics, this letter will be published in *The Diabetic Journal*, and although the Association's policy is never to intervene between patient and doctor, some patients may bring this letter to their doctor's notice.

The Ministry of Health has confirmed that in the case of hardship, application may be made to the National Assistance Board for help.

R. D. LAWRENCE
Chairman, Executive Council,
British Diabetic Association.

London, W.1.

SPONTANEOUS BLEEDING IN HÆMOPHILIA

SIR,—From the correspondence I received after reporting the postoperative bleeding trends in hæmophilic patients with and without spontaneous hæmarthroses,[1] and the absence of Bridge anticoagulant in the Von Willebrand syndrome,[2] it appears that many believe that *spontaneous* bleeding and hæmarthrosis are constant and early features of hæmophilia and Christmas disease. The following data indicate that this is not the case.

Incidence.—Out of 268 cases of hæmophilia and Christmas disease registered at the Manchester Royal Infirmary in January, 1960, whose age-distribution is given in table I, nearly 27% were completely free of spontaneous lesions. The low level of Bridge anticoagulant supported this observation in all cases examined. In those with no apparent family history, the possibility of a blood-clotting defect was considered only after excessive bleeding was produced by trauma or surgery; tooth extraction was always followed by bleeding for at least 48 hours. In the group (73%) with spontaneous lesions, each patient seems to have his own type(s) of bleeding episodes which invariably recurred in the same pattern. Table II shows the distribution of spontaneous hæmorrhagic manifestations among these patients.

Age of occurrence.—Spontaneous hæmorrhage from the alimentary and urinary tracts tends to occur after the age of 17 years, while bruising, hæmarthrosis, and epistaxis are most likely to develop earlier (table II).

Role of Bridge anticoagulant.—A high concentration of this blood-clotting inhibitor has been found in the plasma of patients with spontaneous bleeding episodes.[3] Whether or not these episodes are preceded, or accompanied, by a rise in the anticoagulant level has not yet been established. Further work using Bridge anticoagulant neutralising agent [4 5] may help to clarify this point.

Prevention.—In preventing spontaneous hæmorrhagic episodes in hæmophilia and Christmas disease the following two points are important:

(*a*) The removal of antihæmophilic globulin or Christmas injected factor from circulation, no matter what the dosage, is so rapid [6] that in order to suppress such episodes completely, injections of these factors would be required at least daily. This, apart from being impracticable, is beyond our present resources. Injections at longer intervals, although they may alleviate a coincidental attack, will certainly not stop spontaneous lesions recurring, as shown by Alexander and Landwehr [7] in 4 hæmophilic patients, and by my own experience of 4 cases of Christmas disease, who received plasma transfusions at intervals of 10–17 days for nearly 4 years.

(*b*) Patients with spontaneous bleeding have a high level of Bridge anticoagulant. The action of this blood-clotting inhibitor can be hindered in vitro by Bridge anticoagulant neutralising agent. Accordingly, it would be worth carrying out a clinical trial with this substance to study whether it is effective in preventing these disabling attacks.

Blood Transfusion Centre,
Brentwood, Essex. F. NOUR-ELDIN.

TABLE I—AGE-DISTRIBUTION OF 268 CASES OF HÆMOPHILIA AND CHRISTMAS DISEASE

Age-group (years)	With spontaneous bleeding episodes	Free of spontaneous lesions
<10	51	21
10–19	55	18
20–29	31	13
30–39	24	8
40–49	16	5
50–59	6	4
60–69	12	2
70+	1	1
Total	196	72

TABLE II—FREQUENCY OF DIFFERENT TYPES OF SPONTANEOUS BLEEDING (196 CASES)

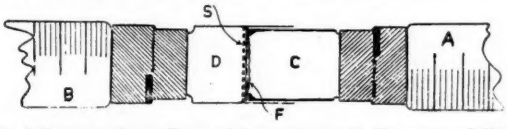
Types of bleeding	Patients affected	Age at first attack
Bruises (subcutaneous and muscular)	160	During childhood
Hæmarthrosis*	192†	Before 17 yr (except 12)
Epistaxis*	78	Before 17 yr (except 4)
Alimentary tract*	36	After 17 yr (except 4)
Hæmaturia*	29	After 17 yr (except 3)
Teething-time bleeding	18	—
Retroperitoneal hæmorrhage ..	14	All ages
Hæmothorax	2	Over 21 yr
Intracranial bleeding	5	All ages
Hæmatocele	0	—

* 80 patients suffered a combination of hæmarthrosis and one or more of the other 3 types of bleeding marked.*
† 1 joint affected, 81; 2 joints affected, 68; more than 2 joints involved, 43.

FILTER FOR ATTACHMENT TO A SYRINGE

SIR,—We devised a somewhat similar device to the one Dr. Anderson (Jan. 14) described for filtering fat and bone spicules out of bone-marrow suspensions.

The filter-chamber [8] has two parts, C and D (see figure), 4·9 cm. long when assembled, of 9 mm. external diameter, and



A: delivery syringe; B: receiving syringe; C, D: parts of filter-chamber; F: filterpaper; S: sieve.

7 mm. internal diameter. One part (C) fits into the other and can be held there by pressure or, preferably, by fitting a screw-thread. In the other part (D) there is a sieve (S). A punched-out disc of filterpaper of appropriate size (7 mm. diameter) is held against the sieve by part (C).

Both parts are fitted with Luer-Lock needle heads. The filter-chamber is attached to two Luer-Lock syringes (A & B) and the fluid to be filtered is introduced into syringe A and

1. McIntyre, H., Nour-Eldin, F., Israëls, M. C. G., Wilkinson, J. F. *Lancet*, 1959, ii, 642.
2. Wilkinson, J. F., Nour-Eldin, F., Israëls, M. C. G. *ibid.* 1958, ii, 115.
3. Nour-Eldin, F., Wilkinson, J. F. *Brit. J. Hæmatol.* 1958, **4**, 292.
4. Nour-Eldin, F. Seventh European Congress of Hæmatology. London, 1959.
5. Nour-Eldin, F. *Lancet*, 1959, ii, 1035.
6. Nour-Eldin, F. Symposium on Blood-clotting factors. *4th Int. Congr. Biochem.* 1958, p. 17.
7. Alexander, B., Landwehr, G. *J. Amer. med. Ass.* 1948, **138**, 174.
8. Nashat, F. S., Yassin, A. K. *J. Fac. Med. Iraq.* 1959, **1**, 166.

forced through the filter-chamber by positive pressure in syringe A or by negative pressure in syringe B.

Department of Physiology,
College of Medicine,
Baghdad, Iraq.

F. S. NASHAT
A. K. YASSIN.

MYOCARDIAL ELECTRODES AND THE DANGER OF VENTRICULAR FIBRILLATION

SIR,—In your issue of May 6 Dr. Noordijk and others describe ventricular fibrillation brought on by foreign currents flowing through the myocardial electrode. Using the same equipment ('Electrodyne' PM-65 pacemaker-monitor) we have observed similar phenomena.

After placing a catheter electrode in a 44-year-old woman with Stokes-Adams syndrome, we were making permanent wiring connections using a soldering iron. With the iron plugged into the mains, ventricular fibrillation was induced when the heated tip was brought into contact with the intracardiac lead. Although the ohmmeter showed a high degree of insulation of the tip from the element of the soldering iron the induced voltage was sufficient to produce the effect. Recovery was spontaneous and the soldering was completed without trouble on stored heat with the plug disconnected.

It became obvious that this effect could be produced by other line-operated apparatus in contact with the patient's body (electrocardiograph, electrically elevated bed, appliances, &c.) where a connection from the earthed side of the PM-65 was made directly to the myocardium. With a bipolar lead in the heart this cannot be avoided. However, by using a unipolar lead to the myocardium, and by ensuring that the indifferent subcutaneous electrode is attached to the earthed side (Black Alligator clip lead with the PM-65) of the pacemaker, any foreign currents would flow from the point of contact through the tissue to the subcutaneous electrode, and have little effect on the heart.

It is essential with bipolar electrodes to earth the electrocardiograph or other offending device to the earthing post on the PM-65, thus removing any chance for a potential gradient to be set up and this is a wise added precaution even with unipolar systems. Such an earthing wire is provided with the instrument.

Royal Victoria Hospital,
Montreal.

L. DAVID PENGELLY
G. A. KLASSEN.

DISTINCTION AWARDS

A correspondent writes:

"The accompanying table shows the percentages of consultants in England and Wales in each specialty who were receiving an award on Dec. 31, 1960: specialties have been rearranged in order of frequency with which awards are given. Differences are not necessarily significant, but the form of this table suggests comparisons more readily than the plain figures of your parliamentary report of May 20 (p. 1122)."

Specialty	No. of consultants	Percentage with awards				
		A plus	A	B	C	All awards
Neurology	82	3·7	11·0	20·7	31·7	67·1
Thoracic surgery	93	4·3	9·7	22·6	28·0	64·5
General medicine	883	2·0	7·7	17·1	30·6	57·4
Neurosurgery	61	6·6	6·6	16·4	26·2	57·4
Plastic surgery	58	1·7	1·7	22·4	29·3	55·2
General surgery	872	2·3	5·6	15·9	29·9	53·8
Pædiatrics	214	0·9	6·1	14·5	27·6	49·1
Infectious diseases	37	—	2·7	8·1	35·1	45·9
Obstetrics	450	2·0	4·0	6·7	25·1	43·1
Orthopædic surgery	348	1·7	4·0	12·0	20·7	38·5
Dermatology	147	0·7	2·7	11·6	18·4	33·3
Ear, nose, and throat	308	—	4·2	9·4	18·8	32·5
Diseases of chest	299	—	4·7	7·4	19·7	31·8
Radiotherapy	126	2·4	3·2	7·9	16·7	30·2
Ophthalmology	301	0·7	4·3	8·3	15·0	28·2
Pathology	725	1·0	3·7	7·0	13·9	25·6
Radiology	477	0·4	1·9	4·6	14·5	21·4
Dentistry	264	0·4	1·5	4·9	13·3	20·1
Venereology	75	—	—	2·7	16·0	18·7
Physical medicine	89	—	1·1	2·2	12·4	15·7
Anæsthetics	828	0·4	0·7	3·3	10·1	14·5
Mental Health	679	0·6	0·7	4·4	8·7	14·4
All specialties	7416	1·2	3·9	9·8	19·6	34·5

Obituary

ALEXANDER GREIG ANDERSON

K.C.V.O., M.A., M.D., LL.D. Aberd., F.R.C.P., D.L.

Sir Alexander Anderson, whose death on May 20 we announced last week, was consultant to Aberdeen Royal Infirmary and a former physician to the Royal Household in Scotland. His medical parish ran from Caithness to Forfar, and colleagues and patients all over the North East of Scotland will remember his skill and kindness.

He was born in the heart of Buchan at Auchnagatt, deriving on the spear and distaff side for several generations from sturdy farming stock. From Robert Gordon's College, Aberdeen, he proceeded to the university there, graduating in arts and medicine. He already showed the stamp of leadership and was elected by his fellow students as president of the Students' Representative Council. After qualifying he filled posts as house-physician and held a fellowship in cancer research, graduating M.D. with honours in 1914. His career was interrupted by a severe chest infection from which he made a good recovery, but during the 1914–18 war he was placed in a Home Service category. Despite this, when an Aberdeen unit—the 43rd General Hospital—arrived in Aldershot with several vacancies on its staff, he was able, with some influence, to join it as assistant physician and proceeded to Salonika, where he soon became major in charge of the medical division of the hospital of 2000 beds, the youngest divisional medical officer in the Macedonian Army. After two years he was invalided home, but a fortunate vacancy occurred and he was appointed an assistant physician to Aberdeen Royal Infirmary in 1919. Later he joined the staffs of the Sick Children's Hospital, and Morningfield Hospital for chronic disease. In 1930 he was elected F.R.C.P. In 1936 he became physician to His Majesty's Household in Scotland and for his services was appointed C.V.O. in 1951 and promoted K.C.V.O. in 1955. He received the honorary degree of LL.D. from his university in 1949 and was appointed deputy lieutenant of Aberdeenshire in 1952.

MacMahon

His services as a consultant were in constant demand, but he readily accepted other responsibilities. The teaching duties which fall naturally to a physician in a teaching hospital he accepted as a task demanding his full powers. The response of his students was immediate and overwhelming—both in the hospital and in his home where he kept open house for them. His clinics and those more homely sittings gained for him numberless devoted followers.

In the administrative sphere he was equally busy. For 23 years he sat on the university court where his wealth of experience and wise counsel were invaluable, and where he constantly upheld the interests of the students. As director of the Royal Infirmary and chairman of the Maternity Hospital board, he was the same wise counsellor, and under the National Health Service he was a member of the North East Regional Hospital Board and a member of the Endowments Commission for Scotland.

But his incursion into social medicine perhaps gave him greater satisfaction and pride than even his success in

pure medicine. He founded the Aberdeen Old People's Welfare Council and, after the usual disappointments and setbacks, set up five homes and old folks' clubs, and in 15 years, practically unaided, gathered over £250,000 for this work.

One of his former students writes:

"A. G. was a big man with something of the presence of a Raeburn portrait of a great Scottish judge, and for generations of students and practitioners his clinical wisdom, especially as a neurologist, seemed unfailing. It was high ambition to become his houseman and, for the less favoured, remembered pride to hear his approbation in that slow, deliberate, slightly rasping voice. He had the assurance of one who knew his worth and few doubted, or dared to doubt it. But he also had a lively sense of humour, wide tolerance, and surprising sympathy for the difficulties of the young. A medical student who had fidgeted in bored discomfort through an abstruse inaugural lecture by a new arts professor turned to his companion and said, "That was a gey queer lecture; I didn't understand a b . . . y word." He was tapped on the shoulder from behind and the horrified youth turned to see A. G. and hear the measured voice, 'Young man, I am a lot older than you, but I didn't understand a b . . . y word either'.

"A. G. used to drive a very large car, but to save the country's petrol in the war he bought a bicycle. One day a tyre became soft and he dismounted and hailed a passing youth who was wearing a medical school scarf. 'Come here, boy, blow up my tyre.' The youth obeyed at once, and A. G., thanking him, asked how he was getting on with his studies. It turned out that the lad was a bank clerk who had borrowed a brother's scarf. Only A. G. could command help in this way and still be greatly loved and admired. Staff and students visited his home in shoals where they drank his beer in privileged and attentive delight. On retiring from the hospital he still worked hard for the university which he loved and for the welfare of old people, but he disliked the word geriatrics and it would be a pity if he was chiefly remembered for the excellence of the city's homes for the elderly. He was a physician and teacher in the tradition and with many of the fine qualities of David Ferrier and Ashley Mackintosh."

R. R., one of his oldest friends, writes:

"Save on formal occasions or by complete strangers he was never called Sir Alexander; to his colleagues, students, friends, and indeed the community at large, he was simply A. G. His amazing generosity was well known, and those of us who knew him best could tell of students, young doctors, nurses, and other patients not only treated without fee or reward, but having nursing-home expenses mysteriously met, and the personal comfort of themselves and relatives overseen; and for every case we knew about there were many we never heard of and which A. G. himself had forgotten till reminded in later life.

"His broad humanity was shown especially at the bedside. Whether the patient was a shy, scared, somewhat stolid country loon (whom A. G. could address in homely doric) or an intellectual or man of title, to whom the rather superstitious dread of the doctor and the fear of disease and pain are often as real as to the other, A. G.'s approach was equally effective. He inspired confidence and hope alike in patient and friends, and left behind that hallmark of a good doctor—a house that was a brighter place for his visit. And with all his success he mingled dignity with humility. A complete stranger might see only the dignified side, most of us saw the other. He was the first to admit error of judgment by himself or to condone it in others and as a result he had innumerable friends and few if any detractors.

"Throughout his career he has been the Nestor of the profession here, to whom all turned in their difficulties, their joys, and their sorrows, and no-one ever came to him for advice or help to be turned empty away. So we in the North East take leave of A. G. A great man, a great physician, a staunch and beloved friend and colleague."

ELIZABETH BOLTON

C.B.E., M.D. Lond.

Miss Elizabeth Bolton, consulting surgeon to the Elizabeth Garrett Anderson Hospital and a former dean and president of the London (Royal Free Hospital) School of Medicine for Women, died on May 25, at the age of 82.

She was born at Leeds, where her father was a Congregational minister, and educated at Stoneygate College, Leicester, and Bedford College, London. She qualified from the London School of Medicine for Women, as it was then called, in 1904. After holding house-appointments at the Royal Free and elsewhere, she graduated M.D. in 1907 and three years later she was appointed to the staff of the Elizabeth Garrett Anderson Hospital.

In 1931 she was appointed dean of the London School of Medicine for Women. Her term of office included the difficult war years. Students and staff of the school and hospital were scattered at times as far afield as St. Andrews, Aberdeen, Exeter, St. Albans, and Arlesey, but throughout the war there was a nucleus of staff and students in London. To maintain continuity of training and the tradition of a medical school in these circumstances was no light task, and Miss Bolton was indefatigable in her efforts and unsparing of herself, taking long journeys which involved considerable hardship and inconvenience. When the school returned to London in 1944 and was hit by a V2 bomb in 1945 she was one of the casualties. Nevertheless, she was active in making arrangements for the students' training to continue in other medical schools, and within four days the students were back at work. When she retired from the deanship in 1945 she was elected president of the school and held this office till 1957.

M. E. L. writes:

"I was appointed to the staff of the Elizabeth Garrett Anderson Hospital in 1921, and as assistant surgeon assisted Miss Bolton at her operating sessions in accordance with the existing traditions. I did this for almost twenty years and the happy and stimulating association between us left an indelible impression on my mind. Her surgical technique was of the highest order and her teaching capacity was of immense help to many generations of students. During the years that she was dean she showed great insight into the character of the students and a deep appreciation of their problems. She was particularly helpful to them when they were scattered far and wide out of London during the war. Her colleagues of the Elizabeth Garrett Anderson Hospital who worked with her at Oster House Hospital, St. Albans, during the war will remember her initiative and drive in converting this institution into a first-class teaching unit.

"She was an outstanding personality among medical women of her time. She set a high standard for herself and insisted on similar standards from all who worked with her. She rendered great and unselfish service to the advancement of the hospital where she worked and the school of medicine which she administered. She will be remembered by the patients she treated so ably, by her medical colleagues, nursing staff, and officials of the Elizabeth Garrett Anderson Hospital, but above all by the many students of the Royal Free Hospital who passed through her hands and benefited from her advice and sympathetic understanding."

K. G. L.-W. writes:

"Elizabeth Bolton was forthright in her manner and so obviously sincere and in some ways uncompromising, that she made a lasting impression on the students of her era and set them a standard which they were not likely to forget. She set them an example of a high degree of diagnostic skill and of the doctor's responsibilities to patients and their relations. She never performed a major operation without seeing the patient alone; thus making sure that the patient was fully aware of the implications and would feel free to discuss any fears or doubts. Few of her students will forget her aphorisms and her insistence that 'patients must never be told anything but the truth, not necessarily all of it, or all of it at once'. They will remember too her kindliness, her Scots humour, and her intensely human interest in the problems of both her students and her patients.

"Her interest in the affairs of the School of Medicine, her colleagues on the clinical, academic, and administrative staffs, and the students was undiminished by her retirement from the office of dean. As president of the school she attended meetings regularly until 1957 when ill health forced her to resign. Even then her interest was unflagging and she was always delighted to have news of all those she knew and remembered."

GEORGE HENDERSON STEVENSON

C.B.E., M.C., M.B. Edin., F.R.C.S.E., F.R.F.P.S.

Mr. George Stevenson, honorary consulting surgeon to the Glasgow Royal Infirmary, died on May 8 at the age of 73. Over his long career his greatest interest was the repair of the effects of trauma, and he played an important part during the late war in setting up a department of orthopædic surgery at the Infirmary.

He graduated from Edinburgh University in 1910 and during the 1914–18 war served as a surgical specialist with the British Expeditionary Force. For his work he was awarded the Military Cross, and the Médaille de la Reconnaissance Française and appointed O.B.E. In the course of his service with No. 2 casualty-clearing station he helped to train many surgical specialists and Harvey Cushing, newly arrived in France, was attached to Stevenson for a time in order to learn something from his military experience. An extension of his military service, at the Ministry of Pensions Hospital at Bellahouston in Glasgow, led to his appointment to the surgical staff of Glasgow Royal Infirmary in 1922, and in this hospital his constantly evolving interest and skill in the treatment of traumatic injury led directly to the foundation of the department of orthopædic surgery in 1940. He was also consultant surgeon to the Princess Louise Hospital, Erskine, where he proved his devotion and affection for disabled ex-Service men. He was promoted C.B.E. in 1958.

W. A. M. writes:

"George Stevenson was a tall, broad, powerfully built man, handsome in appearance, thoughtful and intelligent, a little reserved in his manner. His physical and mental strength was the basis of a kindly gentleness which was quite characteristic. He was constantly spoken of and quoted by his associates and innumerable friends and never without affection. It seems as if he was quite incapable of ungenerous or unsympathetic thought, speech, or action. He was admired and esteemed by his medical students and rightly so, for he took a pride in his teaching and he did it well, and for the students his interest and affection were almost paternal and quite inexhaustible. In his teaching he was never carried away by transient enthusiasms for the latest unsupported theories. He was profoundly well informed, but his teaching was kept in focus and perspective and he gave the greatest emphasis to matters which he believed to be of fundamental importance, to be soundly established and of wide application. As an examiner, too, he would strenuously oppose any attempt to assess the candidate's ability on a basis of his knowledge of obscure and esoteric facts.

"George Stevenson's character and interests were noble in their sweep. His impregnable integrity attracted the trust and affection of all who came in contact with him, and responsibilities were thrust upon him rather than sought. He was a very good surgeon indeed and an excellent diagnostician, as one would expect a man of such broad humanity to be.

"He was a very happy family man and to be entertained in his home was a memorable pleasure. He was a sportsman, supporting Scottish rugby football with enthusiasm. He loved country life and he was able to enjoy it right until the end, and was on a fishing trip to Melvich in Sutherland when he died."

RUDOLPH GEORGE ABERCROMBIE

M.D. Cantab., D.T.M.

Dr. R. G. Abercrombie, late medical director of the Edgar Allen Institute, Sheffield, died in Sheffield on May 14 in his 89th year.

He qualified in 1900, graduated M.B. at Cambridge in 1902, and in 1910 proceeded to the M.D. He was appointed medical director of the Edgar Allen Institute in 1911, and, apart from a period from 1914 to 1918 when he was on war service, he remained director till his retirement in 1950. He was appointed anæsthetist to the Sheffield Royal Hospital in 1913, assistant physician in 1917, and orthopædic physician in 1920.

A. D. writes:

"In 1911 Mr. Edgar Allen, a Sheffield industrialist and philanthropist who was much impressed by the results at the various Zander institutes in Sweden, decided that this treatment should be available to the Sheffield public. Following the acquisition of premises Dr. Abercrombie was appointed its first medical director, and spent several months in Stockholm studying the methods of treatment. He engaged suitable staff, and on Nov. 6, 1911, the Institute was opened. Under Abercrombie's enthusiastic direction its success was rapid, and it has since then made a notable contribution to the treatment of injuries and rheumatic diseases by physical methods.

Abercrombie, like his distinguished brothers the late Lascelles and Sir Patrick Abercrombie, was possessed of a fine intellect. Great as was his knowledge of medicine, his interests ranged widely. He was deeply learnèd in botany and geology. In fishing and shooting he excelled, and continued enjoying them till well beyond his 80th year. Quick and witty, he had a striking personality and was a delightful companion. Though he has outlived most of his contemporaries he will be long remembered."

FRANK EDWARD CHESTER-WILLIAMS

M.R.C.S., F.F.R.

Dr. F. E. Chester-Williams, medical director of the Bradford Regional Radium Institute, died in Bradford on May 12 at the age of 60.

After qualifying from St. Bartholomew's Hospital in 1924, he held junior appointments in London before going to Bradford. Of his life there A. H. writes:

"From 1928, Dr. Chester-Williams was responsible for the development of radiotherapy in Bradford. The Bradford Radium Institute, opened in 1943, of which he was justly proud, is an excellent example of a well-designed radiotherapy unit and has been much admired.

"An energetic worker at his clinical duties, he devoted much time to hospital administration, a field in which his advice was frequently sought; and as a chairman he could be relied upon to conduct the proceedings efficiently and quickly. He was a former president of the Bradford Medico-Chirurgical Society and, until forced by illness to give up most of his outside activities, a staunch supporter of the North of England branch of the British Institute of Radiology, of which he was at one time chairman.

"He loved angling, and children; when a small child appeared at a busy outpatient session, everything stopped while he and the child enjoyed one another's company. A generous man, with a keen sense of good fellowship and a ready wit, he had a considerable reputation as a raconteur and an after-dinner speaker, and he was a delightful host.

" At the memorial service in Bradford Cathedral on May 16, many came from all walks of life to pay their last tribute to one who was greatly admired and respected."

Dr. Chester-Williams is survived by his widow and two sons.

WILLIAM ALLENDALE SANDERSON

M.A. Oxon.

THE administration of the great scientific Trusts is today an important, if vicarious, branch of research; and Mr. Allendale Sanderson, through his work as the first secretary of the United Kingdom and British Commonwealth branch of the Calouste Gulbenkian Foundation and earlier as an assistant director of the Nuffield Foundation, made valuable contributions to medicine. He died on May 21 at the age of 48.

After graduating from St. John's College, Oxford, he spent three years with an advertising agency. During the late war he served in the Intelligence Division of the Admiralty and on the staff of the Supreme Allied Commander, South East Asia, with the rank of lieut.-commander. In 1945, soon after he was demobilised, he joined the staff of the Nuffield Foundation, and from 1945 to 1955 he was also assistant secretary to the Nuffield Provincial Hospitals Trust. One of his special interests was the welfare of the elderly, and he was a past secretary of the National Corporation for the Care of Old People, and European secretary of the social research committee of the International Association of Gerontology. He was a member of the editorial board of the *Twentieth Century*. He was appointed to the staff of the Gulbenkian Foundation in 1956.

G. McL. writes:

" Although, or perhaps because, he was a classicist by discipline, Allen Sanderson was ever ready to seek a deeper understanding of the scientific subjects he was preparing and reviewing for the trustees. His ability to absorb knowledge quickly was sometimes astonishing and a never-failing source of admiration. This knowledge he used not only to interpret the implications of an abstruse scientific or sociological application, but also to help the worthy applicant to make a more persuasive case. These aspects of the work of the secretariat of Foundations and Trusts are perhaps not too well known, but one of Allen Sanderson's gifts was to carry out this work superbly well and, like the artist he was, without any seeming effort. Many people who are doing research in biochemistry, rheumatism, and gerontology have reason to be grateful to him, but his interests went much wider than these subjects, and he has an enormous circle of friends and acquaintances working in most branches of science. This arose, of course, from another of his many attributes—his ability to strike up excellent relations with all sorts and conditions of people. He had all the social graces in full measure and a zest for life. His professional successes were based on a happy home life in which his essential gentleness of character found special expression in his love of children."

Mr. Sanderson leaves a widow, two sons, and two daughters.

Appointments

BASS, B. H., M.D. Lond., M.R.C.P.: part-time consultant physician, Lichfield, Sutton Coldfield, and Tamworth hospital group.

CRORIE, JAMES, M.B. Glasg., F.R.F.P.S.: consultant physician in geriatrics, Motherwell/Hamilton area, main duties at Cleland Hospital.

GARDNER, P. S., M.D. Lond., DIP. BACT.: consultant virologist, United Newcastle upon Tyne Hospitals.

HOLMAN, R. L., M.B. Leeds: assistant pathologist (S.H.M.O.), City General Hospital, Sheffield.

MORGAN, ROGER, M.B. Lond., D.P.M.: director of rehabilitation and medical superintendent, St. Wulstan's Hospital, Malvern.

PIRRIE, ROBERT, M.B. Glasg., M.R.C.P.E., consultant physician, Glasgow Royal Infirmary.

Lancashire County Council:

BREAKELL, JEAN M., M.B. Manc.: divisional M.O., Ashton-under-Lyne area.

DAVIES, A. B., M.B. Wales: divisional M.O., Mossley area.

MILLION, RAYMOND, M.B. Manc., D.C.H.: divisional M.O., Royton/Crompton area.

Notes and News

THE FAMILY DOCTOR AND THE HEALTH VISITOR

A JOINT working party of the College of General Practitioners and of the Royal College of Nursing have been considering what part the health visitor should play in the general practice of the future.[1] Both colleges believe that the more blurred the division between preventive and curative medicine becomes, the more closely she must work with the G.P. It has been suggested that while she remains a local-authority employee, under the administration of the medical officer of health, it may be difficult to draw her into the framwork of general practice; but the working party consider that this problem can be solved, and they give six proved patterns of successful cooperation. Though it often seems that there are not enough health visitors, the shortage may be more apparent than real. For instance, if a health visitor is freed from extraneous tasks, allowed to spend all her time in medicosocial work, and given a motorcar, she can, besides her ordinary health-visiting duties, give all necessary help to a group practice of three doctors. The colleges strongly urge that health visitors should be attached to practices wherever possible or—failing this—that regular meetings and consultations between G.P.s and visitors should be arranged.

SURGICAL AFTERCARE UNIT

BETWEEN the time of operation and discharge there is a period when a surgical patient requires very little nursing care and is largely able to look after himself. He can then be moved from a fully staffed hospital to a simpler unit.

Torrance House, Kilmarnock,[2] was opened two years ago to fill this need. A former sanatorium, it has 44 beds, 28 surgical and 16 medical. Patients are transferred from Kilmarnock Infirmary when they are ambulant, can wear their own clothes, and are fit enough to walk to the diningroom and dayrooms. This is usually three days after a herniorrhaphy or appendectomy, and four or five days after a gastrectomy, or cholecystectomy; but each case is assessed individually.

The surgical wards, for 16 men and 12 women, are four-bed cubicles; they open on to a sun veranda. There are separate dayrooms for men and women, with radio and television; the men's dayroom also has a dartboard and billiards table. Torrance House has its own garden.

The aim has been to reduce the " hospital atmosphere " to a minimum; colour has been freely used, and all surgical dressings are carried out in a separate treatment room.

The nursing staff includes a matron, 2 sisters, 1 full-time staff-nurse, 5 part-time staff-nurses, 1 assistant nurse, and 4 auxiliary nurses. There are no resident doctors, but the aftercare unit is only ten minutes by car from the main hospital, and a ward-round is done daily by a consultant, with his registrar and houseman.

A comparison of costs suggests that at least £4 and possibly nearer £8 per week per patient is saved by looking after them in the aftercare unit. The patients are removed from the busy acute ward, and their rest is undisturbed by noise and night admissions; and transfer to pleasant surroundings hastens their recovery.

EFFICIENCY SHARED

TODAY nearly all regional hospital boards and most teaching hospitals have work-study officers on their staff, and at the Ministry of Health there is a central organisation and methods unit. To pool experience gained, the Ministry is to publish a series of *Abstracts of Efficiency Studies in the Hospital Service*

1. The G.P. members were: Dr. G. Swift, Dr. John Horder, Dr. R. Murray-Scott, Dr. R. M. S. McConaghey, Dr. R. Harkness, Dr. R. J. F. H. Pinsent, and Dr. Richard Scott. The report is published in the *Journal of the College of General Practitioners*, and reprints may be had from the Royal College of Nursing, Henrietta Place, London, W.1 (1s. post free).
2. Ralston, G. J., Scoular, G. H. *Hlth. Bull.* 1961, **19**, 21.

to which all hospital authorities have been asked to contribute by supplying brief details of studies they have undertaken and found rewarding. The first seven *Abstracts* have now appeared and include studies of the delivery of specimens to a pathological laboratory (no. 4), photographic reproduction of reports in a pathology department (no. 5), the layout of a dispensary (no. 6), and the transport system of a hospital group (no. 7). A further six will be published about the end of June, and it is intended to continue to publish sets quarterly. They are obtainable from H.M. Stationery Office and the annual subscription is 12*s.* 6*d.*, including postage.

CONFERENCE OF EDITORS OF MEDICAL-SCHOOL JOURNALS

A conference of editors of medical-school journals, arranged by the *Journal of the Royal Army Medical Corps*, was held at the Royal Army Medical College, Millbank, London, on May 27. Major-General W. R. M. Drew, commandant of the College, took the chair in the morning. Sir Francis Walshe, editor of *Brain*, told of "the trials of a medical editor"; Dr. A. M. Cooke, editor of the *Quarterly Journal of Medicine*, described "how to write for a medical journal"; and Dr. W. A. R. Thomson spoke on "medical journalisms as a career". In the afternoon, Dr. Thomson was chairman of a discussion on the problems of medical student-editors. The *Practitioner* entertained the 35 participants to dinner.

RUSSIAN DRUG INDEX

MANY drugs developed elsewhere have been renamed in the U.S.S.R., and some indigenous Soviet preparations are little known in other countries. In an index [1] lately published the Russian names are listed, with American synonyms, composition, a short description of properties, and references to the literature. In the index, the synonyms as well as the Russian names are set out alphabetically, so the Soviet equivalent of any Western drug can thus be rapidly found. The list was compiled from Soviet medical works published between 1950 and 1960 received by the National Library of Medicine in Washington. It will be invaluable to anyone making a study of Soviet therapeutics.

THE ISLAND OF TERRIBLE FRIENDS

DURING the Italian campaign of 1943, Dr. J. R. Rickett, then a major in the R.A.M.C., is posted to the island of Vis (Lissa) off the coast of Yugoslavia near Split. Surrounded by German-held islands, Vis changes, while Major Rickett is there, from a defensive to an offensive base, from which the partisans and British commandos mount attacks on the Germans.

Major Rickett has to organise a surgical unit from scratch. His difficulties and triumphs are entertainingly described [2] by Mr. Scrutton, whose racy style captures the atmosphere very well.

The "terrible friends" are the partisans, whose attitude to the war—understandable in a people which has seen its country subjugated—was more embittered and ruthless than ours. But the story has many useful lessons—in particular the sorting of mass casualties, and how to organise a hospital from nothing—which make it profitable reading.

University of Cambridge

The degree of M.B. has been conferred on J. D. Geddes.

The Sir Lionel Whitby medal for 1959–60 has been awarded to C. W. M. Adams.

University of Liverpool

Dr. Harold Wilson has been appointed senior lecturer in pharmacology.

1. Russian Drug Index. By S. JABLONSKI and R. M. LEONARD. Washington, D.C.: U.S. Department of Health, Education, and Welfare, Public Health Service publication no. 814. 1961. Pp. 103. Obtainable from the Superintendent of Documents, U.S. Government Printing Office, Washington 25, D.C. 60 cents.
2. The Island of Terrible Friends. By BILL STRUTTON. London: Hodder & Stoughton. 1961. Pp. 192. 15*s.*

University of London

At recent examinations for the degrees of M.B., B.S. the following were successful:

Honours.—Anne C. Berry (*e*), Middlesex; L. M. Blendis (*b*), Middlesex; A. J. Bonn (*e*), St. Bartholomew's; T. J. H. Clark (*b*), Guy's; M. H. Devereux (*a*), Guy's; R. M. B. Dowling (*b*), London; David Faro (*d*), University College; Audrey J. E. Flower (*e*), Middlesex; John Gerwat (*d*), St. George's; G. J. T. Lewis (*c*), University College; Ann-Mary E. Macdonald (*d*), St. Bartholomew's; C. S. Ogg (*b*), Guy's; Ilfra J. Pink (*c*), University College; D. S. Reeves (*d*), Westminster; Linda M. Skolar (*a*, *c*, *e*, *university medal*), Middlesex; G. H. Smith (*d*), St. Mary's; G. P. Williams (*d*), Guy's; F. J. Woodroffe (*d*), King's College.

(*a*) *Distinguished in pathology;* (*b*) *distinguished in medicine;* (*c*) *distinguished in applied pharmacology and therapeutics;* (*d*) *distinguished in surgery;* (*e*) *distinguished in obstetrics and gynæcology.*

Pass.—M. F. A'Brook, Katherine J. Adcock, Michael Aidoo, Suleiman Al-Khedheri, Betty J. Allen, C. D. Allen, R. T. J. Allen, Kathleen M. Allsopp, Eli John Joseph Almeida, Kwasi Ametewee, A. C. Antcliff, P. P. Anthony, Ann P. Appleby, R. F. Armstrong, Roma S. Ashby, Lesley B. Ashworth, D. A. Aubrey, J. C. C. Ayling, Hiram Baddeley, Rosemarie A. Baillod, B. L. Baker, J. S. Ball, J. L. K. Bankes, Alexandra L. H. Barber, Eric Barker, G. Barlow, Judith A. Barnard, Bernice M. S. Barnett, J. J. D. Bartlett, T. P. Bartlett, C. G. Beardwell, H. B. Begg, M. S. Bell, A. R. Bellau, C. L. Berry, D. B. Berzon, A. C. Bird, C. G. Bird, M. B. J. Bishop, Martin Black, Sheena Blackburn, Frances M. Blydenstein, Anne J. V. Boardman, C. J. Bolt, R. A. Bond, Mavis A. Bonnard, C. A. Booth, H. C. Booth, J. C. Bouch, J. M. H. Boyce, Lorna W. Bratton, P. J. Brewer, H. W. E. Briscoe, A. J. Bron, E. J. Brown, Joseph Brown, Lorna A. Brown, R. N. Brownfield, D. A. Bryan, William Bunting, C. R. Campin, R. A. N. Caplan, J. W. Carswell, E. J. P. P. F. Caruana-Galizia, Shirley G. Castle, M. E. Cavendish, Heather C. Chapman, Margaret W. Childe, Isaac Nwaduruoha Chima, K. F. Chittenden, J. Chung Kwai Choy, P. J. Clarkson, N. G. Cockman, S. L. Cohen, Christine M. Colley, J. M. Collis, Jane E. Colliss, N. B. E. Cooter, Penelope A. Cove-Smith, D. R. Covington, W. S. C. Cox, D. R. Dadge, D. G. Daniel, Judith M. Darmandy, Gillian Davey, D. L. Davies, J. D. Davies, M. J. Davies, R. P. Davies, D. M. Denison, Suresh Bhimbhai Rambhai Desai, Hemang Mani Acharya Dixit, Margaret J. Dixon, Reginald Dixon, R. J. Donnelly, J. A. Dormandy, P. J. Doust, F. P. T. Drake, R. M. Drake, A. M. Driscoll, Maureen B. Duggan, Joy B. Edelman, R. S. Edmondson, D. F. Elson, C. W. Elston, D. A. Evans, C. V. Everard, P. R. H. Evison, R. W. T. Farley, M. J. Farr, Barbara V. Faulk, Ten Feizi, R. H. Fell, T. J. ffytche, I. T. Field, C. J. Fielding, Shirley M. Fisher, J. M. T. Ford, Richard France, Stuart Gallannaugh, R. H. Gandy, S. W. Garland, Adi Framroze Gazdar, Vera Gellert, Mohammad Ali Nakhai Ghods, B. V. Gill, H. M. Gillespie, L. J. Goldfine, Kathleen M. Goodwin, D. N. Gordon, Rosamund Gould, Sally M. Grantham, Judith Greenwood, B. W. Griffiths, D. J. Grundy, D. G. Gwyn, J. D. Hailstone, Jennifer M. Hall, J. H. Hall, M. S. Hall, J. F. Hallpike, R. E. Hamill, Ruth Hamilton, J. A. Hanne, I. W. Hanwell, J. C. Harding, M. W. Harper, N. P. A. L. Harper, D. L. Harris, Deirdre A. Hart, J. C. D. Hart, I. C. Harvey, D. J. Hatch, W. E. Hawes, Judith M. Hawker, T. J. Hawkins, P. M. Hayward, Shafiq Hazboun, D. C. Herbert, E. B. Herd, Penelope B. Hewitt, Doreen M. M. Heyworth, B. M. Hogbin, Tessa Holman, J. T. Holmes, Hilary J. Honey, John Hood, A. P. Hopkins, Alisa Hornung, Barbara J. Horrell, P. M. B. Howard, Margaret E. Hughes, Kathleen M. Hunt, W. J. Hunter, L. A. Hurt, D. W. Hyatt, Michael Indech, Angela M. H. Jackson, Marianne Janosi, M. I. V. Jayson, Anne M. Jequier, D. L. Johns, M. G. Johnson, P. M. Johnson, B. M. Jones, Tibor Kajtar, R. G. Kay, Susan Kay, Anne B. Kenshole, Heather S. Kerr, Penelope J. Key, D. E. L. King, M. H. King, N. J. W. Kippax, Veronica Kirton, Coral R. Knight, Ebenezer Krotelai Korley, Heather Lachlan, W. A. Landers, Eileen Larkin, R. G. C. Lett, Cynthia N. A. Levett, W. A. Lindsay, A. J. Lines, Jennifer Lloyd, Barbara V. Longley, T. J. McCarthy, Mary B. MacKeith, Jean McKinnon, Fatemeh Elaheh Madjd, A. C. J. Maendl, Micheline M. Maher, J. K. C. Maile, D. E. I. Mais, Cynthia M. Marcon, R. H. Marston, D. J. Martin, J. P. Martin, M. H. J. Martin, C. A. S. Mason, David Mathias, B. F. Meggitt, Lucy Mensah, D. S. Miller, Helen R. Miller, Malcolm Millington, Diana E. Millward, Mary C. Milne, Patricia J. Money, Maldwyn Morgan, Ruth M. Morris, P. R. Mortimer, D. B. Moss, Julia A. Munro, Malcolm Murray, Judith C. Naylor, Pauline M. Naylor, J. M. Nocton, P. M. J. O'Donnell, P. M. O'Driscoll, Joseph Adjei Ogyaadu, N. J. Osborn, B. W. Otridge, Adrian Padfield, M. E. Paul, R. H. Pearce, Margaret Pedlar, R. A. Peebles, M. C. Owen Phillips, M. C. Pietroni, Margaret N. R. Pitt, Dorothy E. Platts, J. O. M. Pobee, A. J. Poole, Bernadette M. V. Porter, E. W. Powell, G. A. Prall, Albert Prestwich, M. G. Prinn, W. G. Prout, W. E. M. Pryse-Phillips, B. W. Pullen, Margaret Pyke, D. C. Quantock, M. C. Rallings, R. G. Rathbone, Kathleen F. Rayner, A. J. Reed, C. P. Reynolds, Janis M. Richmond, D. M. Ricks, Joyce M. Robinson, Valerie A. Rogers, Joy G. Roworth, Jane D. D. Rowswell, Bridget A. Rylands, Kwame Safo-Adu, Sankar Sahai, J. B. Sales, R. W. Salmon, A. H. Sarafian, S. H. Saunders, Raphael Jizchak Schick, André Schulman, David Shaffer, A. B. Shaw, Brenda N. Shaw, Andreas Carl Felix Sjögren, Vivienne A. Skinner, M. A. Skivington, D. H. Smith, H. D. Smith, Jacqueline Q. Smith, P. N. Sperryn, T. A. Spratley, T. N. Stanbridge, S. L. R. Stanton, Dennis Steel, D. L. Stevens, Ray Stilwell, Norman Stoddart, Edward Stonehill, J. C. H. Strachan, Margaret E. Tamblyn, Angela C. Telfer, A. C. Templeton, G. M. Theobald, L. K. H. Therkildsen, G. O. Thomas, Valerie J. Thomas, W. H. F. Thomson, A. E. Thorn, J. G. B. Thurston, K. A. Turner, Sophie S. Turner, Elizabeth J. Tytler, Rosemary A. Underhill, J. M. Varney, J. P. Vaughan, Frances Wahl, Panela G. Wales, B. A. Wallace, B. B. Wallace, Sheila L. Waller, Barbara C. Walsh, E. R. Walrond, J. B. Watkins, B. M. Watson, Michael Watson, L. M. Webber, A. D. Wedderspoon, Sally K. Weeks, D. J. Westlake, T. K. Wheeler, D. C. Whyte, D. H. Wickenden, B. T. Williams, Margaret Williams, C. E. R. Winer, B. E. P. Wookey, B. J. Woolford, R. J. Worden, Ann F. Worsfold, Adela W. Wright, I. G. Wylie, Caroline R. S. M. Wynne-Roberts, Edward Young, M. A. Zatouroff.

Royal College of Surgeons of England

The Wolfson Foundation has made a grant of £250,000 to the college in recognition of its work in this country and in the Commonwealth overseas. The gift will be primarily used to furnish and equip the Hunterian museum, which is now being rebuilt after its destruction by bombing and which is expected to be finished by the spring of 1962.

University of Sheffield

A refresher course for general practitioners is to be held during the week beginning Monday, Sept. 25. Further details will be found in our advertisement columns.

University of Bristol

A chair of mental health is to be established in the university which will be endowed by donations from the Van Neste Foundation and from the late Mrs. Norah Cooke-Hurle. The Foundation has close ties with the National Spastics Society, and its trustees include Dr. C. P. Stevens, director of the society, who conceived the idea of a professorship of mental health with special facilities for research into preventable mental illness. Dr. Stevens and Mr. Van Neste have handed over to the university on behalf of the Foundation the first of four cheques for £15,000 for the endowment of the chair.

The new department of mental health will take the place of the present department of psychiatry. The professor will have a part-time staff of 1 lecturer, 2 tutors, and 11 teachers. He will have 24 beds in the South Western Region Hospital Board area and 2 outpatient sessions each week in Bristol.

Royal College of Obstetricians and Gynæcologists

At a meeeting on May 27, with Mr. A. C. H. Bell, the president, in the chair, the following were elected to Council:

As representatives of the fellows: John Campbell McClure Browne, Richard Glyn Maliphant, Robert Newton, Ninian McIntire Falkiner.
As representatives of the members: Edward Anthony John Alment, George Barton Gibson.

The following were admitted to the fellowship:

H. B. Bagshaw, Duncan Ballantine, S. J. Behrman, Fred Benjamin, D. C. A. Bevis, Constance L. Beynon, J. M. Bowen, G. C. Brentnall, Alexander Broido, A. D. H. Browne, Ellsworth Cullen Bryant, A. D. Byrne, Walter Calvert, Kate I. Campbell, Leslie A. Cruttenden, Gilbert Dalley, Jyotsna Dei, N. E. C. de la Hunt, J. C. R. Dunlop, M. P. Embrey, I. B. Faris, H. D. Freeth, G. T. Gibson, J. H. Gibson, A. B. Hay, R. E. Hemsley, J. B. Hurll, R. G. Law, T. L. T. Lewis, Una G. Lister, W. J. McCord, W. G. MacGregor, Margaret A. Mackie, Robin Murdoch, C. G. Paine, Edward Parry-Jones, Peng Teik Por, Lilian Raferty, Sangarapillai Ranjanayagam, W. D. Refshauge, K. S. Richardson, H. A. Ripman, Henry Roberts, C. G. Roworth, Everall M. Shippam, W. R. Sloan, D. F. Smith, A. B. Stenhouse, P. C. Steptoe, Agnes M. Stewart, A. S. B. Studdy, G. S. Thomas, J. G. Thurston, Ewart Williams, E. A. Williams.

The following were admitted to the membership:

A. G. Amias, Jean L. Baker, D. C. Beckingham, N. A. Beisher, F. R. Betheras, Paresh Chandra Bhattacharjya, Eunice Ruth Burton, Ramaswamy Chandravadana, Sin Giap Chua, Evelyn Coates, Aileen F. Connon, Krishna Dar, D. A. Davey, Chitta Samkar Dawn, K. J. Dennis, P. L. C. Diggory, R. B. Dorofaeff, Aly Dawood El-Tannir, J. A. L. F. E. Noel, C. W. Gale, Alan Gillespie, Hans Glietenberg, John Babtist Gnanapragasam, Sek-Mun Goon, J. G. Griffiths, G. H. B. Hart, G. M. Johnstone, Khorshed S. Karai, M. J. A. Kelly, W. J. Kirkpatrick, H. K. Kosasky, Serge Kunstler, D. Youn-Sen Liang, Ma Yin May, Malika Mehra, Ma Khin Nu, Upenda Nath Pathak, Aaron Penn, C. R. Porteous, Thelma Rasalam, Fay M. Rennie, W. J. St. N-G Rhys, Abharani R. y, Irene M. Salmon, Yvonne M. Salmon, Jasu Indravadan Sanghvi, Padma Raju Sathyanadhan, Edwina Sayes, R. J. Seddon, Nirmel Kumar Sen, Pravash Chandra Sen Gupta, Ahmed Abu-el-Futah Shandall, Adige Vedavyass Shenoy, R. V. Stephenson, Sushil Kumar Suppal, Muriel M. H. Sutcliffe, T. C. Svensen, I. P. Thew, G. R. Thoms, V. R. Tindall.

The following have been awarded the D.OBST.:

Abida Abdus-Salam, Michel Assad Aboud, A. H. Abrahams, Ada M. Adams, C. D. Addis-Jones, Adegboyega Folaranmi Adedoyin, Sunil Kumar Adhya, P. M. Aichroth, Kosin Amatayakul, I. F. Anderson, Elvira C. Arya, J. W. Aspinall, P. G. Atkinson, W. J. Atkinson, Ibrahim Farid Ayad, Gerald Baker, Suppiah Balakrishnan, Richard Barker, Elizabeth M. Beattie, J. H. Bell, R. J. M. Bell, Angus Bennett, J. W. Bennett, P. C. Bewes, Tulsi Assandas Bhambhani, Joan Bishop, R. Y. Bishop, W. I. K. Bisset, R. C. Blake, J. W. Bland, A. R. Bowie, J. R. Bowles, Miriam J. B. Brady, Mary E. Braithwaite, E. C. Bramwell, Harold Brenner, M. F. Brewster, Anthony Brickman, Helen B. Brodie, Dorothy A. Brown, J. S. Brown, W. F. Brown, Michael Budd, A. E. Bullock, Maureen V. Burrage, Hazel M. Burtenshaw, R. M. Burton, Mervyn Busson, Kathleen Calder, J. P. R. Campbell, R. M. Carr, A. J. Chalmers, Deoram Khandoo Chaudhari, J. J. S. Chesser, J. H. Cole, R. J. Cole, F. B. Coleman, Hellen Stephen Conn, B. J. E. Cooke, A. M. Cotton, W. G. R. Couldrick, D. D. Craig, J. C. Creedon, J. D. Crosbie, R. E. Cudmore, D. P. Cummine, R. L. C. Cumming, A. H. Davies, E. G. L. Davies, R. J. L. Davis, Gisele Marie Madeleine de Lane Lea, Sinniah Dharmalingam, Rashida Mohammad Din, Elizabeth C. Dobie, J. D. Donnelly, N. J. T. Donelly, J. C. Doran, R. F. Dorrington, Allison C. Dunbar, Anthony Dunnill, M. K. Dunstan, Colin Dunster, P. C. E. Edgecombe, T. G. Egan, F. R. Ellis, Sunfei Theodore Eng, J. A. F. Evans, J. B. Evans, K. M. Evans, John Fairley, E. A. Featherby, G. L. Featherstone, D. W. Ferguson, Dorothy Jane Osuman Ffoulkes-Crabbe, R. M. Finch, Joyce Fleming, Lalita M. Fooks, A. L. Freeman, John Fyfe, Brian Gallagher, Louise Gallagher, G. R. Gerson, Sobha Ghosh, Vahine Gibbings, J. R. M. Gibson, Robert Gillespie, E. W. Gillison, J. B. Glass, R. P. Golding, J. E. Goodess, K. J. Green, A. R. Grieve, Jane M. B. Griffiths, Margaret A. Griffiths, P. R. Grob, L. H. Grove, J. D. L. Hall, A. C. Halliwell, J. S. H. Hamilton, R. J. Hamilton, R. D. Harbinson, J. W. Harcup, A. W. Harcus, Alexander Harley, A. G. H. Heaney, J. D. Henderson, W. J. M. Hood, P. J. Hook, Maldwyn Hopkin-Thomas, Rimon Gotthelf Hornung, Helen M. Hoyle, J. D. W. Hunter, J. M. Hunter, R. J. Hunter, Bertram Igbogbahaka, E. H. Innes, J. J. Irvine, N. J. Jackson, Nesta B. James, G. H. C. Jenkins, A. C. Johansson, I. C. Johnson, G. D. Jones, Jane M. Jones, Modest Clarence Jones, Susan P. Jones, R. A. Jupe, Balakrishnan Kamalamma, L. M. Kearney, A. G. Kerr, M. J. Kettle, F. F. P. Kierans, Shirley J. Knight, Jan Antoni Kuzemko, Gwenda D. Larkin, B. H. Latimer, P. A. Lawrence, Barbara J. Ledsom, B. L. Lees, O. C. Legg, G. F. Lewis, T. S. Little, Cynthia Lucas, A. M. Lush, Michael Lydon, William McConnachie, I. A. Macfarquhar, A. J. Mackintosh, W. D. Mackay, K. S. A. Mardgwick, Frank Mansfield, Ronald Marks, N. C. Marshall, Sheila C. Martin, Ann R. Matthews, A. J. Membrey, R. B. Miller, M. R. R. Moore, D. L. Morrison, Richard Moulton, Phillipa N. Mourant, Gillian K. Mucklow, F. H. Muir, J. S. Munro, P. J. Murphy, A. I. S. Murray, I. M. Murray, Mary A. Murray, Soe Myint, Jahan Ara Naqshbandi, J. J. Nattrass, C. H. Naylor, Khin Khin Ne, Ben Totham Jervois Newland, J. C. Nicholson, J. L. Nimmo, Khin Khin Nu, C. F. O'Connor, E. L. Offerman, George Fleming Rhind Ogilvie, C. J. M. O'Keeffe, Razia Omar, Lilian L. Orba, B. W. G. Orr, J. T. Outred, Haroon Rashid Owadally, R. K. H. Parker, W. F. Parrott, Hasmukhrai Manmohanda Patel, Lalita Amrit Patel, Usha Thakorbhai Patel, J. F. Patrick, Christine M. Peacock, P. E. Pearce, G. N. Penlington, C. R. Phillips, Eileen B. Phillips, R. W. Porter, Michael Priest, L. W. Purnell, N. A. Purry, C. E. Emanuel Puvimanasinghe, Durgapursad Ramprotol, S. A. Rance, Raymond Randall, Shanta Vadilal Rangwala, A. J. Reeves, T. J. Richards, C. J. Riley, Michel Elias Rivlin, N. A. Robinson, T. R. Robinson, B. K. Rogers, Jessie M. A. Rogerson, D. W. Ross, G. B. Ross, Elizabeth Rowe, G. C. Rowe, Gargi Rughani, Paul Sadler, Phillida Alfreda Sampson, D. N. Seaton, D. W. Seldon, Kantilal Talakchand Shah, Sadiqua Gulmohomed Shaikh, Edward Shaoul, Olive P. Sharp, A. G. Sherman, Miru Hashmatrai Shivdasani, N. L. Short, Glennys S. Shute, Saida Siddiqi, M. W. Smillie, J. C. S. Smith, J. N. Smith, R. R. Smith, Simon Spragge, Anne E. Staddon, D. M. Stainton-Ellis, J. F. Steele-Perkins, D. G. Strachan, D. J. Strath, M. J. Streule, I. T. Stuttaford, R. M. Swinburne, G. W. Tapper, A. R. Tappin, Margaret Taylor, Chinnamma Thomas, D. H. Thomas, William Thomson, Jill M. Thwaites, R. E. Tonge, V. L. Tosh, J. E. C. Twentyman, Benedict Chukwudi Uzodik, Zarina Iqbal Ramzan Vellani, Perampalam Vithiananthan, Anna G. Walker, I. W. Wallace, G. G. Ward, A. V. R. Watson, Peter Watson, Margaret J. Watt, W. N. Waugh, J. N. Webb, Wallace White, Alan Whitworth, Glenwynne Williams, J. B. Williams, C. J. F. L. Williamson, G. T. Wills, J. O. Woods, H. G. Wotherspoon, Heather E. Wright, Margaret E. G. Wright, J. D. Wyatt, R. J. Wylie, K. E. Young.

Welsh National School of Medicine

Mr. B. E. D. Cook, reader in dental medicine at Guy's Hospital Dental School, has been appointed professor of oral medicine and dean of dental studies. He will take up his appointment on Aug. 1, 1962, in preparation for the new dental school and hospital planned to be built in Cardiff.

Society of Apothecaries of London

On June 20 at 8.30 P.M. in the hall of the society, Black Friars Lane, E.C.4, the gold medal in therapeutics will be presented to Prof. Ralston Paterson.

At recent examinations the following were successful:

L.M.S.S.A.—B. Alam, B. J. Cooper, D. G. Else, M. Gunasheela, C. R. Jayachandra, D. M. Laugharne, D. C. Prior, S. H. A. Razvi, S. E. Tchamouroff, S. B. Wassif.

D.I.H.—R. J. D. Abraham, A. J. Childs, E. G. Clark, C. M. S. Coppin, W. H. G. Davies, M. T. Fernandes, F. J. G. Kinsella, S. E. Onejeme, E. Sweeney, C. White.

Faculty of the History of Medicine and Pharmacy.—On April 28 Dr. W. S. C. Copeman, the chairman, awarded the honorary fellowship of the faculty to Sir Arthur MacNalty and Sir Zachary Cope. In presenting the second annual report, Dr. Copeman said that the membership stood at 304, and 65 universities, medical schools, and postgraduate institutes had enrolled as corporate members.

Application forms for membership of the faculty and of the second British congress on the history of medicine, which is to be held in London on Sept. 28 and 29, may now be had from Dr. F. N. L. Poynter, Wellcome Historical Medical Library, Wellcome Building, Euston Road, London, N.W.1.

Faculty of Ophthalmologists

The following officers have been elected for 1961–62:

President, Prof. G. I. Scott; immediate past president, Mr. E. G. Mackie; vice-presidents, Mr. J. E. M. Ayoub, Mr. P. J. Evans; hon. treasurer, Mr. G. T. Willoughby Cashell; hon. secretary, Mr. J. R. Hudson.

Birmingham Medical Exhibition

Prof. I. E. Bush will open this exhibition at Princes Hall, Broad Street, Birmingham, on June 12 at 2.30 P.M. The exhibition will be open from 11.30 A.M. daily until June 16.

Royal Society of Medicine

The following have been elected to honorary fellowships:

Sir Samuel Bedson, Sir Stanford Cade, Prof. Douglas E. Cannell, Dr. G. B. Dowling, Sir Stewart Duke-Elder, Mr. W. Sampson Handley, Sir David Henderson, Sir Harold Himsworth, Sir Harry Jephcott, Dr. F. H. Krusen, Sir Henry Souttar.

On Friday, July 21, at 2 P.M., the Section of Experimental Medicine and Therapeutics of this society is to hold a public report session at which contributors to the Ciba Foundation symposium on pulmonary structure and function, which is being held from July 18 to 20, will review the proceedings of the symposium.

Postgraduate Medical School of London

A symposium on modern aspects of cardiovascular radiology will be held from Sept. 21 to 23 at the school, Ducane Road, W.12. The titles of the sessions will be acquired heart-disease, congenital heart-disease, pulmonary circulation, hypertension, and peripheral vascular disorders. Application to attend should be made by Aug. 18 to the dean at the school.

Harveian Society of London

At the Buckston Browne and Gray Hill dinner, held at the House of Commons on May 24, The Society was proposed by Mr. Albert Costain, the Member for Harvey's birthplace, Folkestone; and the company included Alderman L. C. Aldridge, whose first day it was as Mayor of Folkestone, an office four times held by Harvey's father. Looking at another centre of Harveian interest, Dr. E. R. Cullinan, the president, said that, thanks largely to the efforts of Mr. Dickson Wright, £7500 had been collected from many parts of the world for the restoration of Hempstead Church in Essex, where Harvey is buried. Mr. Dickson Wright related how the tower fell down in 1883, just after the sexton had wound the clock; but now the bells had been recast, the clock was ready to be wound again, and the vaults had been restored. Another £6500 was still needed to complete the work. Dr. C. S. Treip gave The Guests an agreeable welcome, and Sir Russell Brain replied.

Sir Halley Stewart Trust Lecture

Dr. R. A. Butler is to give this lecture at the Wright-Fleming Institute, St. Mary's Hospital, London, W.2, on Thursday, June 22, at 5.30 P.M. His subject will be problems of the pharmaco-kinetics of anæsthetics.

Henry Head Centenary Celebrations

A meeting to celebrate the centenary of Sir Henry Head's birth is to be held on Aug. 31, at The London Hospital, at 3 P.M. The speakers will be Sir Russell Brain, Dr. Macdonald Critchley, Prof. K. W. Cross, and Dr. R. A. Henson. Those who wish to attend the meeting should notify Dr. Henson, Neurological Department, The London Hospital, E.1, before Aug. 17.

Surgical Congresses in Dublin

The International Society of Surgery will hold a congress in Dublin from Sept. 2 to 9, on the invitation of the Irish Government, and from Sept. 7 it will be joined by the International Cardio-Vascular Society. The two presidents will be Prof. E. Dahl-Iversen, of Copenhagen, and Prof. Charles Rob, now of Rochester, New York, and the general secretary is Mr. T. C. J. O'Connell. A post-congress meeting will be held in Dublin in the following week.

Contracts for Patented Drugs

The announcement by the Minister of Health that he proposed to use section 46 of the Patents Act, 1949, in obtaining certain drugs for the hospital service (see *Lancet*, May 27, 1961, pp. 1154, 1176) was followed by the appearance in the lay Press on May 23 of a notice by the Ministry of Health inviting manufacturers to tender for the supply of the tetracyclines, chlorothiazide and hydrochlorothiazide, and chloramphenicol.

Brigadier T. M. R. Ahern has been appointed honorary surgeon to the Queen in succession to Major-General F. M. Richardson, who has retired.

A course for registered medical practitioners will be held at the London College of Osteopathy, 25, Dorset Square, N.W.1. It will begin in October, and further particulars may be had from the secretary of the college.

The Cambridge Graduates' Medical Club will hold its annual general meeting and dinner at Sidney Sussex College on Friday, June 30. Further particulars may be had from Dr. H. H. E. Batten, F.R.C.S., 67, Bridge Street, Cambridge.

The Ministry of Health's *Hospital Building Note* no. 6 deals with diagnostic X-ray departments. Copies (1s. 6d.) may be had from H.M. Stationery Office.

Diary of the Week

JUNE 4 TO 10

Monday, 5th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Dr. James Sharp: Ankylosing and Rheumatoid Spondylitis.
INSTITUTE OF DERMATOLOGY
4 P.M. (32, Welbeck Street, W.1.) Dr. Leon Szur: Radiotherapy and Malignant Skin Conditions. (Second of two lectures.)
5 P.M. (32, Welbeck Street, W.1.) Mr. Ian Muir: Reconstructive Surgery and Malignant Disease.
INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
4.30 P.M. (Chelsea Hospital for Women, Dovehouse Street, S.W.3.) Mr. Tom Smith: Endometriosis.

Tuesday, 6th

UNIVERSITY COLLEGE LONDON, Gower Street, W.C.1
5.30 P.M. Dr. G. P. Lewis: Bradykinin—its Chemistry, Pharmacology, and role in Physiological and Pathological Reactions.
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Prof. R. S. Speirs: Role of Eosinophils in Inflammation.
INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
3 P.M. (Hammersmith Hospital, Ducane Road, W.12.) Mr. J. A. Stallworthy: Vaginal Hysterectomy.
ST. MARY'S HOSPITAL MEDICAL SCHOOL, W.2
5 P.M. (Wright-Fleming Institute.) Mr. Frank Musgrove: Impressions of Obstetrics and Gynæcology in America.

Wednesday, 7th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Dr. Peter Wildy: Architecture of Viruses.
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.15 P.M. *History of Medicine.* Mr. F. C. Grigg: Anatomical Microslides and Microscopes of the Past Century. Dr. W. E. Foster: Early History of the Microscope in Clinical Practice. Miss Jessie Dobson: John Hunter's Microscope Slides.
8 P.M. *Surgery.* Mr. Rodney Smith, Dr. Kenneth W. Warren (Boston): Surgery of the Pancreas.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. W. Riddell: World Distribution of Fungus Infections.
INSTITUTE OF DISEASES OF THE CHEST, BROMPTON, S.W.3
5 P.M. Dr. W. M. Macleod: Abnormal Transradiancy of One Lung.
CHARING CROSS HOSPITAL MEDICAL SCHOOL, Chandos Place, W.C.2
5.30 P.M. Mr. N. C. Lake: Investigations into the Effect of Cold upon Tissues and Organisms. (Huxley lecture.)
ROYAL FREE HOSPITAL, Gray's Inn Road, W.C.1
5.15 P.M. Sir Horace Smirk (Dunedin): Pathogenesis and Management of Hypertension.
MEDICO-CHIRURGICAL SOCIETY OF EDINBURGH
8.30 P.M. (Royal College of Surgeons, Nicolson Street, Edinburgh.) Dr. J. H. Bowie, Mr. J. S. Jeffrey, Dr. J. M. Murdoch: Hospital Infection.

Thursday, 8th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Mr. Ian Ranger: Functional Anatomy of the Diaphragm, with Special Reference to the Ætiology and Treatment of Œsophageal Hiatus Hernia. (Hunterian lecture.)
POSTGRADUATE MEDICAL SCHOOL OF LONDON
4 P.M. Dr. Raymond Daley: Arteritis.
ROYAL SOCIETY OF MEDICINE
5 P.M. *Ophthalmology.* Prof. J. François (Ghent): Pigmentary Retinopathy. Prof. J. Barraquer (Barcelona): Total Penetrating Corneal Grafts.
HONYMAN GILLESPIE LECTURE
5 P.M. (University New Buidlings, Teviot Place, Edinburgh.) Dr. J. A. Tulloch: Occurrence of Diabetes Mellitus in the Tropics.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Physiology Department, Queen's College, Dundee.) Dr. G. E. Godber: Recent Trends in Specialisation and their Impact on Medical Practice.

Friday, 9th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Mr. G. C. Tresidder: Urological Operations.
4 P.M. Sir Horace Smirk: Hypertension—Treatment and Pathogenesis.
INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
4.30 P.M. (Queen Charlotte's Hospital, Goldhawk Road, W.6.) Sir John Peel: Diabetes in Pregnancy.
FACULTY OF RADIOLOGISTS
3 P.M. (University College Hospital Medical School, W.C.1.) Annual General Meeting.
4.30 P.M. Dr. Felix G. Fleischner (Boston): Pulmonary Embolism with and without Infarction. (Opening of 2-day meeting.)